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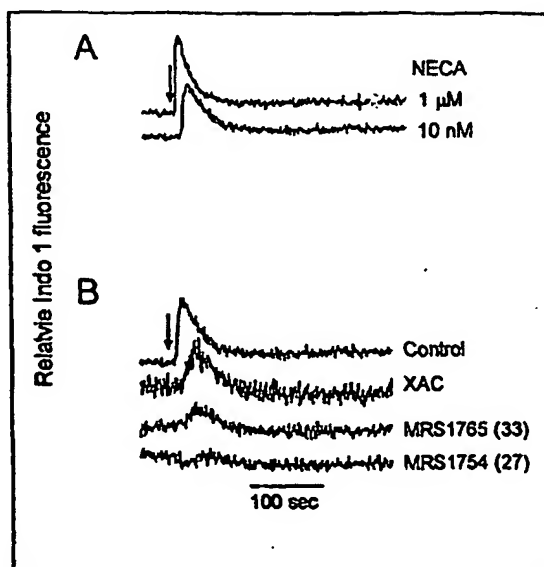
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(54) Title: SUBSTITUTED 8-PHENYLXANTHINES USEFUL AS ANTAGONISTS OF A_{2B} ADENOSINE RECEPTORS(57) Abstract: The present invention provides compounds and pharmaceutical compositions that are selective antagonists of A_{2B} adenosine receptors (ARs). These compounds and compositions are useful as pharmaceutical agents.



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**SUBSTITUTED 8-PHENYLYXANTHINES USEFUL AS
ANTAGONISTS OF A_{2B} ADENOSINE RECEPTORS**

5

Cross-Reference to Related Applications

This application claims priority of U.S. provisional patent applications Serial Nos. 60/136,898 filed June 1, 1999, 60/136,900 filed June 1, 1999, 60/151,875 filed August 31, 1999, and 09/505,504 filed February 17, 2000.

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Field of the Invention

The present invention relates to compounds and pharmaceutical compositions that are selective antagonists of A_{2B} adenosine receptors (ARs). These compounds and compositions are useful as pharmaceutical agents.

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Background of the Invention

The alkylxanthine theophylline (compound 1, Figure 1), a weak non-selective adenosine antagonist (See Linden, J., *et al.*, in *Cardiovascular Biology of Purines*, eds. G. Burnstock, *et al.*, 1998, pp 1-20.) is useful therapeutically for the treatment of asthma. However, its use is associated with unpleasant side effects, such as insomnia and diuresis. (See Vassallo, R. *et al.*, *Mayo. Clin. Proc.* 1998, 73, 346-354.) In recent years, the use of theophylline as a bronchodilator, for relief of asthma, has been supplanted by drugs of other classes, *i.e.*, selective β_2 -adrenergic agonists, corticosteroids, and recently leukotriene antagonists. (See Drazen, J. M., *et al.*, *New Eng. J. Med.* 1999, 340, 197-206.) These compounds also have limitations, thus, the development of a theophylline-like drug with reduced side effects is still desirable.

30

It has been recognized that theophylline and its closely related analogue caffeine block endogenous adenosine acting as a local modulator of adenosine

receptors in the brain and other organs at therapeutically useful doses.

Adenosine activates four subtypes of G protein-coupled adenosine receptors (ARs), $A_1/A_{2A}/A_{2B}/A_3$. (See Fredholm, B. B., *et al.*, *Pharmacol. Rev.* 1999, 51, 83-133.) In comparison to the other known actions of theophylline, *e.g.*,

- 5 inhibition of phosphodiesterases, theophylline is more potent in antagonism of adenosine receptors. Enprofylline, (compound 3, Figure 1) a compound that is used to treat asthma, is another example of a xanthine that has been reported to block A_{2B} adenosine receptors. However, this compound only weakly blocks A_1 , A_{2A} and A_3 adenosine receptors.

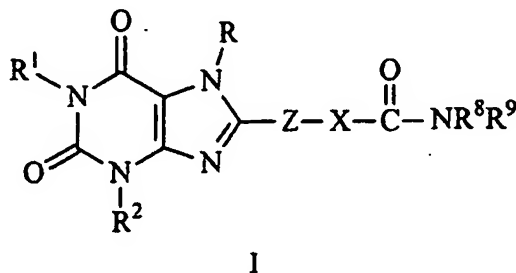
- 10 It has been reported that therapeutic concentrations of theophylline or enprofylline block human A_{2B} receptors, and it has been proposed that antagonists selective for this subtype may have potential use as antiasthmatic agents. (See Feoktistov, I., *et al.*, *Pharmacol. Rev.* 1997, 49, 381-402; and Robeva, A.S., *et al.*, *Drug Dev. Res.* 1996, 39, 243-252. Enprofylline has a
- 15 reported K_i value of 7 μ M and is somewhat selective in binding to human A_{2B} ARs. (See Robeva, A.S., *et al.*, *Drug Dev. Res.* 1996, 39, 243-252 and Linden, J., *et al.*, *Mol. Pharmacol.* 1999, 56, 705-713.) A_{2B} ARs are expressed in some mast cells, such as the BR line of canine mastocytoma cells, which appear to be responsible for triggering acute Ca^{2+} mobilization and degranulation. (See
- 20 Auchampach, J.A., *et al.*, *Mol. Pharmacol.* 1997, 52, 846-860 and Forsyth, P., *et al.*, *Inflamm. Res.* 1999, 48, 301-307.) A_{2B} ARs also trigger Ca^{2+} mobilization, and participate in a delayed IL8 release from human HMC-1 mast cells. Other functions associated with the A_{2B} AR are the control of cell growth and gene expression, (See Neary, J., *et al.*, *Trends Neurosci.* 1996, 19, 13-18.) endothelial-
- 25 dependent vasodilation (See Martin, P.L., *et al.*, *J. Pharmacol. Exp. Ther.* 1993, 265, 248-253.), and fluid secretion from intestinal epithelia. (See Strohmeier, G.R., *et al.*, *J. Biol. Chem.* 1995, 270, 2387-2394.) Adenosine acting through A_{2B} ARs has also been reported to stimulate chloride permeability in cells expressing the cystic fibrosis transport regulator. (See Clancy, J.P., *et al.*, *Am. J.*
- 30 *Physiol.* 1999, 276, C361-C369.)

Although adenosine receptor subtype-selective probes are available for the A_1 , A_{2A} , and A_3 ARs, only few weakly selective antagonists and no selective

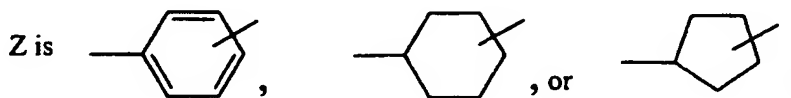
agonists are known for the A_{2B} receptor. Therefore, a continuing need exists for compounds that are selective A_{2B} receptor antagonists.

Summary of the Invention

- 5 The present invention provides compounds that act as antagonists of A_{2B} adenosine receptors. Accordingly, the present invention provides a compound of formula I:



- wherein R, and R¹ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl,
 10 (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, heterocycle, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or heteroaryl;



- X is (C₁-C₈)alkylene, (C₂-C₈)alkenylene, (C₂-C₈)alkynylene, wherein one of the
 15 carbon atoms in the alkylene, alkenylene or alkynylene groups can be replaced with a group having the formula —O—, —N(R⁴)C(O)—, —OC(O)—, —N(R⁵)(R⁶)—, —S—, —S(O)— or —SO₂—, wherein

- R² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₃-C₈)heterocycle, (C₆-C₁₀)aryl, (C₆-C₁₀)heteroaryl, (C₄-C₁₆)cycloalkylalkyl or (C₇-C₁₈)aralkyl, optionally substituted
 20 with one or more substituents selected from the group consisting of —OH, —SH, —NH₂, —NHR⁷, —CN, —CO₂H, and —SO₃H, wherein

R^4 , R^5 , R^6 and R^7 are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl or halo (C_1-C_6) alkyl, wherein R^8 is hydrogen, (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, (C_7-C_{18}) aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; or

R^8 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

R^8 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; and

wherein R^9 is $-NR^{10}R^{11}$, or R^9 is (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, (C_7-C_{18}) aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; or

R^9 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

R^9 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$,

$-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$,
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$, and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8) alkyl,
 (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heterocycle,
 5 heteroaryl, $-\text{C}(\text{O})(\text{CH}_2)_n\text{CO}_2\text{R}^{12}$, $-\text{C}(\text{O})\text{CR}^{21}=\text{CR}^{22}(\text{CH}_2)_m\text{CO}_2\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{12}$,
 $-\text{C}(\text{O})(\text{C}_3-\text{C}_8)$ cycloalkyl or $-\text{C}(\text{O})(\text{C}_3-\text{C}_8)$ cycloalkenyl, each optionally
 substituted with one or more substituents, wherein the substituents independently
 are oxo, (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ -
 aralkyl, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$,
 10 $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or
 $-\text{SO}_3\text{H}$; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together
 to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted
 with one or more substituents, wherein the substituents independently are oxo,
 (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl,
 15 heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$,
 $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$;
 wherein n is 1 to 6, and m is 0 to 4;

R^{12} is hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl,
 (C_3-C_8) cycloalkyl, $(\text{C}_4-\text{C}_{16})$ cycloalkylalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, hetero-
 20 cycle, or heteroaryl,

wherein the R^{12} group is optionally substituted with one or more
 substituents independently selected from the group consisting of oxo,
 (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl,
 heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$,
 25 $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$.

The R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{23} and R^{24} groups are
 independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl,
 $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl or halo (C_1-C_6) alkyl; and the R^{21} and R^{22} groups are
 independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl,
 30 $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl.

The invention also provides pharmaceutically acceptable salts of a
 compound of formula I. The invention also provides a pharmaceutical
 composition comprising a compound of formula I or a pharmaceutically

acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

Additionally, the invention provides a therapeutic method for preventing or treating a pathological condition or symptom in a mammal, such as a human, wherein the activity, *i.e.*, over-activity, of adenosine A_{2B} receptors is implicated in one or more symptoms of the pathology and antagonism (*i.e.*, blocking) of their activity is desired to ameliorate said symptoms. Such diseases or conditions include, but are not limited to, asthma, diarrheal diseases, insulin resistance, diabetes, prevention of mast cell degranulation associated with ischemia/reperfusion injuries, inhibition of angiogenesis in neoplastic tissues, and inhibition of angiogenesis in diabetic retinopathy or hyperbaric oxygen-induced retinopathy. The invention also includes a method for treating asthma, diarrheal diseases, insulin resistance, diabetes, inhibition of angiogenesis in neoplastic tissues, and inhibition of angiogenesis in diabetic retinopathy or hyperbaric oxygen-induced retinopathy in a mammal, (*e.g.*, a human) comprising administering to the mammal in need of such therapy, an effective amount of at least one compound of formula I or pharmaceutically acceptable salt(s) thereof.

The invention provides a compound of formula I for use in medical therapy preferably for use in treating diseases or conditions associated with deleterious A_{2B} receptor activation or activity, including asthma, diarrheal diseases, insulin resistance, diabetes, ischemic/reperfusion injury, inhibition of angiogenesis in neoplastic tissues, and inhibition of angiogenesis in diabetic retinopathy or hyperbaric oxygen-induced retinopathy, as well as the use of a compound of formula I for the manufacture of a medicament for the treatment of a pathological condition or symptom in a mammal, such as a human, which is associated with deleterious A_{2B} receptor activation or activity, including the above-referenced diseases or pathologies.

The invention also includes a method comprising contacting a compound of formula I, optionally having a radioactive isotope (radionuclide), such as, for example, tritium, radioactive iodine (for example, ¹²⁵I for binding assays or ¹²³I for Spect Imaging) and the like, with target A_{2B} adenosine receptor sites comprising said receptors, *in vivo* or *in vitro*, so as to bind said receptors. Cell membranes comprising bound A_{2B} adenosine receptor sites can be used to

measure the selectivity of test compounds for adenosine receptor subtypes or can be used as a tool to identify potential therapeutic agents for the treatment of diseases or conditions associated with A_{2B} -receptor mediation, by contacting said agents with said radioligands and receptors, and measuring the extent of displacement of the radioligand and/or binding of the agent.

Brief Description of the Figures

Figure 1 illustrates structures of various xanthines that act as antagonists at A_{2B} receptors.

Figure 2 is a graphic illustration of the inhibition by several selective A_{2B} AR antagonists of NECA-stimulated calcium mobilization in HEK- A_{2B} cells. Cells were loaded with Indo 1 for 1 hour. The A) curves indicate calcium mobilization in response to 10 nM and 1 μ M NECA added at the arrow. The B) curves indicate calcium mobilization in response to 10 nM NECA added at the arrow in cells pretreated for two minutes with 1% DMSO (control) or with 100 nM of the indicated antagonists. The results are typical of replicate experiments.

Figure 3 illustrates the synthesis of amide derivatives of xanthine carboxylic acid congeners of the invention.

Figure 4 illustrates the synthesis of hydrazide derivatives of xanthine carboxylic acid congeners of the invention.

Figure 5 illustrates the synthesis of hydrazide derivatives of xanthine carboxylic acid congeners of the invention.

Figure 6 illustrates the experimental protocol for the ninety minute cardiac left anterior descending (LAD) coronary artery occlusion/reperfusion test. Regional myocardial blood flow was measured at 30 second, 90 second, 3 minute, 5 minute, 8 minute, 13 minute, 23 minute, 38 minute, and 68 minute, intervals, using radioactive microspheres (mic), administered at the times indicated.

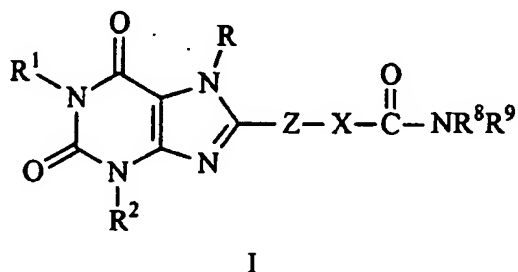
Figure 7 illustrates the regional myocardial transmural blood flow in the central infarct (solid bar), border (open bar), and normal (striped bar) zones at baseline, during the LAD occlusion, and 2 hrs after reperfusion. During the total LAD occlusion, mean flow of test solution was < 0.2 ml/min/g for 90 min.

Figure 8 illustrates the mean infarct size measured using triphenyl tetrazolium chloride (TTC) staining in vehicle-treated (control) dogs and in dogs treated with 8-[4-(((4-cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (27). The *p*-cyanoanilide, 27, (200 nM) was infused intracoronary at a rate of 1 ml/min during occlusion and reperfusion. The treatment prevented or markedly attenuate the extent of myocardial infarction and significantly reduced the infarct area (IA), measured as % left ventricle area (%LV) or % area at risk (%RA).

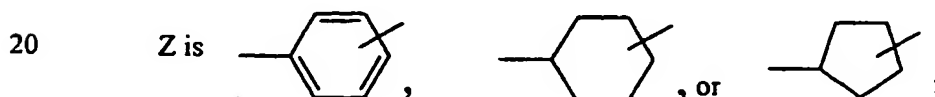
Figure 9 illustrates the results the specific and nonspecific binding of test compound 8-[4-(((4-cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (27). The graph shows both specific and nonspecific binding.

Detailed Description of the Invention

In one embodiment the present invention provides compounds of formula I:



wherein R, and R¹ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₃-C₈)heterocycle, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or (C₆-C₁₀)heteroaryl,



and X is (C₁-C₈)alkylene, (C₂-C₈)alkenylene, (C₂-C₈)alkynylene. In the X groups one of the carbon atoms in the alkylene, alkenylene or alkynylene groups can be

replaced with a group having the formula $-\text{O}-$, $-\text{N}(\text{R}^4)\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{N}(\text{R}^5)(\text{R}^6)-$, $-\text{S}-$, $-\text{S}(\text{O})-$ or $-\text{SO}_2-$, wherein

R^2 is hydrogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{alkenyl}$, $(\text{C}_2-\text{C}_8)\text{alkynyl}$, $(\text{C}_1-\text{C}_8)\text{alkoxy}$, $(\text{C}_3-\text{C}_8)\text{cycloalkyl}$, $(\text{C}_3-\text{C}_8)\text{heterocycle}$, $(\text{C}_6-\text{C}_{10})\text{aryl}$, $(\text{C}_6-\text{C}_{10})\text{heteroaryl}$, $(\text{C}_4-\text{C}_{16})\text{cycloalkylalkyl}$ or $(\text{C}_7-\text{C}_{18})\text{aralkyl}$; optionally substituted with one or more substituents selected from the group consisting of $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NHR}^7$, $-\text{CN}$, $-\text{CO}_2\text{H}$, and $-\text{SO}_3\text{H}$, wherein

R^4 , R^5 , R^6 and R^7 are independently hydrogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{alkenyl}$, $(\text{C}_3-\text{C}_8)\text{cycloalkyl}$, $(\text{C}_6-\text{C}_{10})\text{aryl}$, $(\text{C}_7-\text{C}_{18})\text{aralkyl}$ or $\text{halo}(\text{C}_1-\text{C}_8)\text{alkyl}$.

R^8 is hydrogen, $(\text{C}_3-\text{C}_8)\text{cycloalkyl}$, $(\text{C}_4-\text{C}_{16})\text{cycloalkylalkyl}$, $(\text{C}_7-\text{C}_{18})\text{aralkyl}$, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_1-\text{C}_8)\text{alkoxy}$, $\text{halo}(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{alkenyl}$, $(\text{C}_6-\text{C}_{10})\text{aryl}$, $(\text{C}_7-\text{C}_{18})\text{aralkyl}$, heteroaryl, halo, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; or

R^8 is $(\text{C}_1-\text{C}_8)\text{alkyl}$, substituted with one or more substituents independently selected from the group consisting of oxo, $(\text{C}_2-\text{C}_8)\text{alkenyl}$, $(\text{C}_6-\text{C}_{10})\text{aryl}$, $(\text{C}_7-\text{C}_{18})\text{aralkyl}$, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; or

R^8 is $(\text{C}_6-\text{C}_{10})\text{aryl}$, substituted with one or more substituents independently selected from the group consisting of $(\text{C}_1-\text{C}_8)\text{alkyl}$, $\text{halo}(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{alkenyl}$, $(\text{C}_7-\text{C}_{18})\text{aralkyl}$, heteroaryl, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; and

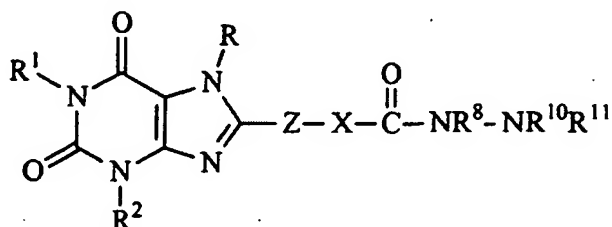
wherein R^9 is $(\text{C}_3-\text{C}_8)\text{cycloalkyl}$, $(\text{C}_4-\text{C}_{16})\text{cycloalkylalkyl}$, $(\text{C}_7-\text{C}_{18})\text{aralkyl}$, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $\text{halo}(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{alkenyl}$, $(\text{C}_6-\text{C}_{10})\text{aryl}$, $(\text{C}_7-\text{C}_{18})\text{aralkyl}$, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; or

R^9 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$,
 5 $-SO_2R^{20}$ and $-SO_3H$; or

R^9 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$,
 10 $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$.

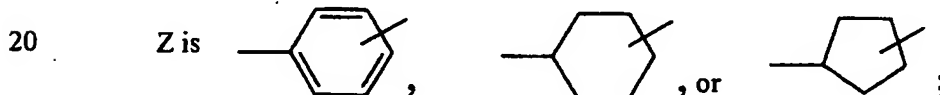
The R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{23} and R^{24} groups are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl or halo (C_1-C_6) alkyl.

In another embodiment the present invention provides compounds of
 15 formula II:



II

wherein R , and R^1 are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_8) alkoxy, (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, (C_3-C_8) heterocycle, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl or (C_6-C_{10}) heteroaryl,



and X is (C_1-C_8) alkylene, (C_2-C_8) alkenylene, (C_2-C_8) alkynylene. In the X groups one of the carbon atoms in the alkylene, alkenylene or alkynylene groups can be

replaced with a group having the formula $-\text{O}-$, $-\text{N}(\text{R}^4)\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{N}(\text{R}^5)(\text{R}^6)-$, $-\text{S}-$, $-\text{S}(\text{O})-$ or $-\text{SO}_2-$, wherein

R^2 group is hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_8) alkoxy, (C_3-C_8) cycloalkyl, (C_3-C_8) heterocycle, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_6-\text{C}_{10})$ heteroaryl, $(\text{C}_4-\text{C}_{16})$ cycloalkylalkyl or $(\text{C}_7-\text{C}_{18})$ aralkyl; optionally substituted with one or more substituents selected from the group consisting of $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NHR}^7$, $-\text{CN}$, $-\text{CO}_2\text{H}$, and $-\text{SO}_3\text{H}$, wherein R^4 , R^5 , R^6 and R^7 are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl or halo (C_1-C_8) alkyl.

R^8 is hydrogen, (C_3-C_8) cycloalkyl, $(\text{C}_4-\text{C}_{16})$ cycloalkylalkyl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, (C_1-C_8) alkoxy, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, halo, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; or

R^8 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; or

R^8 is $(\text{C}_6-\text{C}_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, $-\text{C}(\text{O})(\text{CH}_2)_n\text{CO}_2\text{R}^{12}$, $-\text{C}(\text{O})\text{CR}^{21}=\text{CR}^{22}(\text{CH}_2)_m\text{CO}_2\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})(\text{C}_3-\text{C}_8)$ cycloalkyl or $-\text{C}(\text{O})(\text{C}_3-\text{C}_8)$ cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or

—SO₃H; or the R¹⁰ and R¹¹ groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C₁-C₈)alkyl, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂, —CO₂R¹⁵, —OC(=O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H; wherein n is 1 to 6, and m is 0 to 4;

R¹² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, hetero- cycle, or heteroaryl,

wherein the R¹² group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C₁-C₈)alkyl, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂, —CO₂R¹⁵, —OC(=O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H.

The R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²³ and R²⁴ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or halo(C₁-C₆)alkyl; and the R²¹ and R²² are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl.

Preferred compounds of the invention exclude compounds of formula I wherein —NR⁸R⁹ is aminoalkyl, aminodialkyl or hydrazino. Preferred compounds of the invention also exclude compounds of formula I wherein R and R⁸ are both H, and R¹ and R² are both alkyl, and R⁹ is 2-hydroxyethyl, 2-thiolethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo or iodo. Alkyl, alkoxy, alkenyl, alkynyl, etc. denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such

as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

Heteroaryl encompasses a radical attached via a ring carbon of a
 5 monocyclic aromatic ring containing 5-10 ring atoms, and preferably from 5-6 ring atoms, consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, (C₁-C₄)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom,
 10 particularly a benz-derivative or one derived by fusing a propylene, trimethylene or tetramethylene diradical thereto.

The term heterocycle encompasses a cyclic radical attached via a ring carbon or nitrogen of a monocyclic or bicyclic ring containing 3-10 ring atoms, and preferably from 5-6 ring atoms, consisting of carbon and one to four
 15 heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, (C₁-C₄)alkyl, phenyl or benzyl, and optionally containing 1-3 double bonds (*e.g.*, —CH=CH— or —CH=N—). Heterocycle includes, for example, tetrahydrofuryl, dihydrofuryl, tetrahydroimidazolyl, azanorbornyl, pyrrolidinyl, piperidinyl, piperiziny, and the like.

20 Specifically, (C₁-C₈)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, isopentyl, 3-pentyl, hexyl, heptyl or octyl; (C₃-C₈)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; (C₄-C₁₂)cycloalkylalkyl can be cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl or 2-cyclohexylethyl; (C₁-C₈)alkoxy can be
 25 methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, hexyloxy, heptyloxy or octyloxy; (C₂-C₈)alkenyl can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl or 4-octenyl; (C₂-C₈)alkynyl can be
 30 ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1-heptylnyl, 2-heptylnyl, 3-heptylnyl, 1-octynyl, 2-octynyl or 3-octynyl; halo(C₁-C₈)alkyl can be

iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl or pentafluoroethyl; (C₆-C₁₀)aryl can be phenyl, indenyl or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, 5 pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

The term "amino acid," comprises the residues of the natural amino acids (e.g., Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Hyl, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) in D or L form, as well as unnatural amino 10 acids (e.g., phosphoserine, phosphothreonine, phosphotyrosine, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, citruline, α -methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). The term 15 also comprises natural and unnatural amino acids bearing a conventional amino protecting group (e.g., acetyl, benzyl, COCF₃ or benzyloxycarbonyl), as well as natural and unnatural amino acids protected at the carboxy terminus (e.g., as a (C₁-C₆)alkyl, phenyl or benzyl ester or amide; or as an α -methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled 20 in the art (See for example, Greene, T.W.; Wutz, P.G.M. *Protecting Groups In Organic Synthesis*, Second Edition, 1991, New York, John Wiley & sons, Inc, and references cited therein). An amino acid can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus or through any other convenient point of attachment, such as, for example, through 25 the sulfur of cysteine.

The term "peptide" comprises the residues two or more of the natural amino acids, as well as unnatural amino acids or a mixture thereof, that are linked through an amide bond. The term also comprises peptides that are protected at the carboxy terminus (e.g., as a (C₁-C₆)alkyl, phenyl or benzyl ester 30 or amide; or as an α -methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, Greene, T.W.; Wutz, P.G.M. *Protecting Groups In Organic Synthesis*, Second Edition, 1991, New York, John Wiley & sons, Inc, and references cited therein). A

peptide can be linked to the remainder of a compound of formula I through the carboxy terminus, the amino terminus or through any other convenient point of attachment, such as, for example, through the sulfur of cysteine. Preferably, the peptide has less than 30 amino acid residues, more preferably less than 20

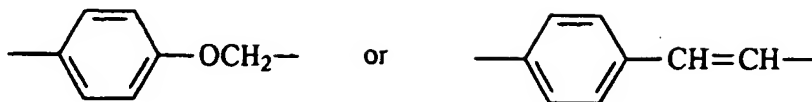
5 residues, and most preferably from about 2 to about 5 residues.

The preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, iso-butyl, and sec-butyl, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, and 3-hexyl. The preferred alkylene groups are methylene, ethylene, propylene, butylene, pentylene, and hexylene. The preferred alkenyl groups are
 10 vinyl, 1-propenyl, 2-propenyl (allyl), 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, and 3-hexenyl. The preferred alkenylene groups are ethenylene, propenylene, butenylene, pentenylene, and hexenylene. The preferred alkynyl groups are ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentynyl, 2-
 15 pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl. The preferred alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, and sec-butoxy. The preferred cycloalkyl groups are cyclopentyl, and cyclohexyl. The preferred cycloalkylalkyl groups are, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopentylethyl, and 2-
 20 cyclohexylethyl. The preferred aryl groups are phenyl, indenyl or naphthyl. The preferred aralkyl groups are benzyl and 2-phenylethyl. The preferred haloalkyl groups are iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl or pentafluoroethyl. The preferred heteroaryl groups are furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiodiazolyl, thiophenyl, pyrazolyl, pyrrolyl, pyrazinyl, thiazolyl, pyridinyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

A specific Z substituent is :



A specific Z—X moiety is:



- 5 Specific R¹ and R² groups are each —CH₂CH₃, —CH₂CH=CH₂, —CH₂CH₂CH₃, or cyclohexylmethyl.

Specific R⁸ and R⁹ groups are each hydrogen, substituted phenyl or benzyl.

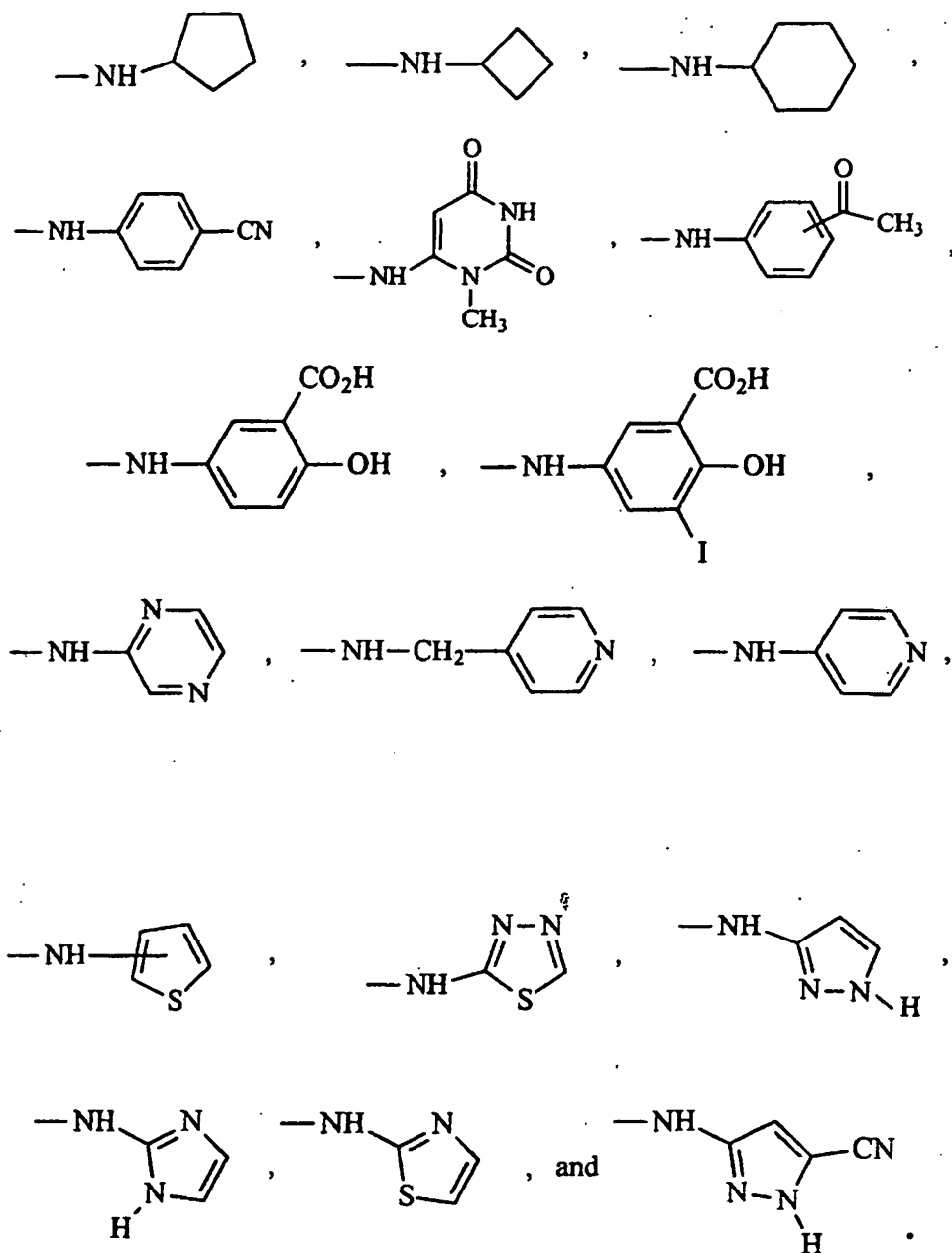
- Specific R⁴, R⁵, R⁶, and R⁷ groups are each hydrogen, methyl, ethyl, propyl, isopropyl, butyl, vinyl, propenyl, butenyl, cyclopentyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl and benzyl.

- In a preferred embodiment, when the R⁹ groups are phenyl substituted with one two or three substituents that are independently cyclopentyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl, benzyl, —OH, F, Cl, Br, I, —CN, —NO₂, —C(O)OR¹⁵, —C(O)R¹⁶, —NR¹³R¹⁴ or —C(O)NR¹⁷R¹⁸ or benzyl they can optionally be methyl, ethyl, propyl, isopropyl, butyl, vinyl, propenyl, butenyl, cyclopentyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl, benzyl, —OH, F, Cl, Br, I, —CN, —NO₂, —C(O)OR¹⁵, —C(O)R¹⁶ or —C(O)NR¹⁷R¹⁸, wherein
- 15 R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are as defined above.

- The preferred R¹⁰, and R¹¹ groups are hydrogen, methyl, ethyl, propyl, isopropyl, butyl, vinyl, propenyl, butenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, phenyl and benzyl, —CO(CH₂)_nCO₂R¹², —COCR²¹=CR²²(CH₂)_mCO₂R¹², —C(O)R¹², —C(O)(C₃–C₈)cycloalkyl, —C(O)(C₃–C₈)cycloalkenyl, and compounds wherein the R¹⁰ and R¹¹ groups and the nitrogen atom taken together form a ring. More preferred R¹⁰, and R¹¹ groups are independently hydrogen, —CO(CH₂)_nCO₂R¹², —COCR²¹=CR²²(CH₂)_mCO₂R¹², —C(O)R¹², —C(O)(C₃–C₈)cycloalkyl and —C(O)(C₃–C₈)cycloalkenyl, each wherein the R¹⁰ and R¹¹ groups and the nitrogen atom taken together form (C₆–C₁₀)heterocycle or (C₆–C₁₀)heteroaryl, n is 1 to 4 and m is 0 to 2. The most preferred R¹⁰, and R¹¹ groups are independently hydrogen, —CO(CH₂)_nCO₂R¹², —COCH=CHCO₂R¹², —C(O)R¹², or wherein the R¹⁰ and R¹¹ groups and the nitrogen atom taken
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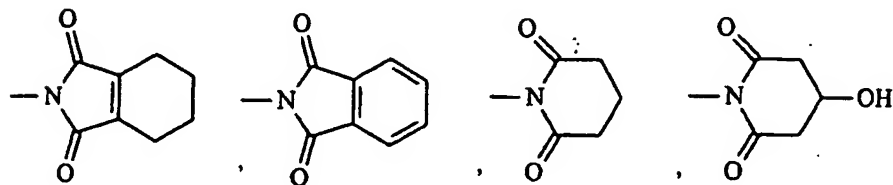
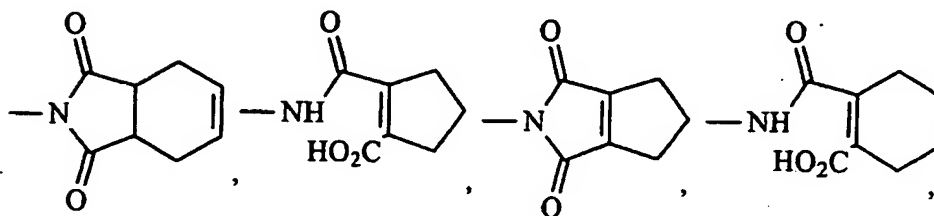
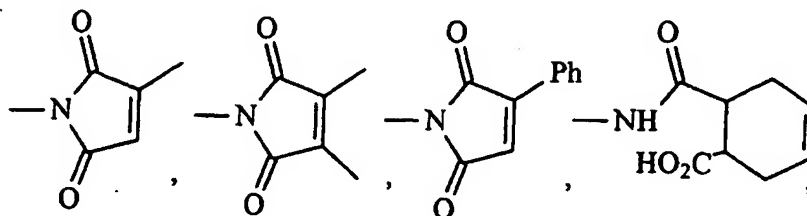
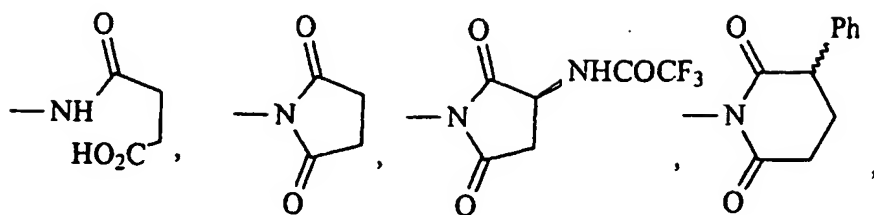
together form a ring or wherein n is 1 to 4 and R^{12} , R^{13} , R^{14} , R^{21} and R^{22} are defined above.

Specific values for $-NR^8R^9$ are:



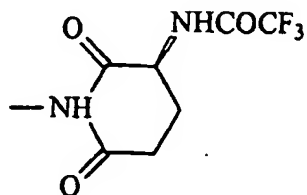
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Specific values for $-NR^{10}R^{11}$ are:



5

or



The following abbreviations have been used herein:

	[¹²⁵ I]ABA	[¹²⁵ I]N ⁶ -(4-aminobenzyl)-adenosine
	[¹²⁵ I]AB-MECA	[¹²⁵ I]N ⁶ -(4-amino-3-iodobenzyl)-adenosine-5'-N-methyluronamide
5	¹²⁵ I-ABOPX	¹²⁵ I-3-(4-amino-3-iodobenzyl)-8-oxyacetate-1-propyl-xanthine
	8-SPT	8-sulphophenyltheophylline
	AR	adenosine receptor
	Bn	benzyl
10	BOP-Cl	bis(2-oxo-3-oxazolidinyl)-phosphinic chloride
	CGS 21680	2-[4-[(2-carboxyethyl)phenyl]ethyl-amino]-5'-N-ethylcarbamoyl adenosine
	CHA	N ⁶ -cyclohexyladenosine
	CHO cells	Chinese hamster ovary cells
15	CPX	8-cyclopentyl-1,3-dipropylxanthine
	DIPEA	diisopropylethylamine
	DMAP	4-dimethylaminopyridine
	DMEM	Dulbecco modified eagle medium
	DMF	N,N-dimethylformamide
20	DMSO	dimethylsulfoxide
	EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
	EDTA	ethylenediaminetetraacetate
	HEK cells	human embryonic kidney cells
	HOBt	1-hydroxybenzotriazole
25	K _i	equilibrium inhibition constant
	NECA	5'-N-ethylcarbamoyladenosine
	NHS	N-hydroxysuccinimide ester
	R-PIA	R-N ⁶ -phenylisopropyladenosine
	SAR	structure-activity relationship
30	TFA	trifluoroacetic acid
	TFAA	trifluoroacetic anhydride
	Tris	tris(hydroxymethyl)aminomethane

XAC	8-[4-[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine
XCC	8-[4-[[[carboxy]methyl]oxy]phenyl]-1,3-dipropylxanthine
5 ZM 241385	4-(2-[7-amino-2-{furyl}{1,2,4}triazolo{2,3-a}{1,3,5}triazin-5-ylaminoethyl)phenol

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis or by chromatographic separation using a chiral stationary phase). It is also conventional to determine A_{2B} adenosine antagonist activity using the standard tests described herein or using other similar tests which are well known in the art.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, *i.e.*, orally or parenterally, by intravenous, intramuscular, topical, inhalation or subcutaneous routes.

Thus, the present compounds may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and

substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

10 The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and
15 stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example,
20 by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for
25 example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the
30 other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying

techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, *i.e.*, when they are liquids. However, it will generally be desirable to
5 administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the
10 present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings or sprayed onto the
15 affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

20 Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet *et al.* (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith *et al.* (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by
25 comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from
30 about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The amount of the compound or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected

but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 $\mu\text{g/kg}$, *e.g.*, from about 10 to about 75 $\mu\text{g/kg}$ of body weight per day, such as 3 to about 50 μg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 $\mu\text{g/kg/day}$, most preferably in the range of 15 to 60 $\mu\text{g/kg/day}$.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 μg , conveniently 10 to 750 μg , most conveniently, 50 to 500 μg of active ingredient per unit dosage form.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.02, to about 5 μM , preferably, about 0.05 to 2 μM , most preferably, about 0.1 to about 1 μM . This may be achieved, for example, by the intravenous injection of a 0.005 to 0.5% solution of the active ingredient, optionally in saline or orally administered as a bolus containing about 1-100 μg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-0.1 $\mu\text{g/kg/hr}$ or by intermittent infusions containing about 1-10 $\mu\text{g/kg}$ of the active ingredient(s).

The compounds of the invention can be administered by inhalation from an inhaler, insufflator, atomizer or pressurized pack or other means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as carbon dioxide or other suitable gas. In case of a pressurized aerosol, the dosage unit may be determined by providing a value to deliver a metered amount. The inhalers, insufflators, atomizers are fully described in pharmaceutical reference books such as Remington's Pharmaceutical Sciences Volumes 16 (1980) or 18 (1990) Mack Publishing Co.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations; such as multiple

inhalations from an insufflator or by application of a plurality of drops into the eye.

The invention will now be illustrated by the following non-limiting Examples.

5

EXAMPLES

Pharmacology.

The ability of a compounds of the invention to act as an A_{2B} adenosine receptor antagonists may be determined using pharmacological models which are well known to the art or using test procedures described below.

The human A_{2B} receptor cDNA was subcloned into the expression plasmid pDoubleTrouble as described in Robeva, A. *et al.*, *Biochem. Pharmacol.*, **51**, 545-555 (1996). The plasmid was amplified in competent JM109 cells and plasmid DNA isolated using Wizard Megaprep columns (Promega Corporation, Madison, WI). A_{2B} adenosine receptors were introduced into HEK-293 cells by means of Lipofectin as described in Felgner, P. L. *et al.*, *Proc. Natl. Acad. Sci. USA*, **84**, 7413-7417 (1987).

Cell culture

Transfected HEK cells were grown under 5% CO_2 /95% O_2 humidified atmosphere at a temperature of 37°C. Colonies were selected by growth of cells in 0.6 mg/mL G418. Transfected cells were maintained in DMEM supplemented with Hams F12 nutrient mixture (1/1), 10% newborn calf serum, 2 mM glutamine and containing 50 IU/mL penicillin, 50 mg/mL streptomycin, and 0.2 mg/mL Geneticin (G418, Boehringer Mannheim). Cells were cultured in 10 cm diameter round plates and subcultured when grown confluent (approximately after 72 hours).

Radioligand binding studies.

At A_{2B} receptors: Confluent monolayers of HEK- A_{2B} cells were washed with PBS followed by ice cold Buffer A (10 mM HEPES, 10 mM EDTA, pH 7.4) with protease inhibitors (10 μ g/mL benzamidine, 100 μ M phenylmethanesulfonyl fluoride, and 2 μ g/mL of each aprotinin, pepstatin and

leupeptin). The cells were homogenized in a Polytron (Brinkmann) for 20 s, centrifuged at 30,000 x g, and the pellets washed twice with buffer HE (10 mM HEPES, 1 mM EDTA, pH 7.4 with protease inhibitors). The final pellet was resuspended in buffer HE, supplemented with 10% sucrose and frozen in aliquots at -80°C. For binding assays membranes were thawed and diluted 5-10 fold with HE to a final protein concentration of approximately 1 mg/mL. To determine protein concentrations, membranes, and bovine serum albumin standards were dissolved in 0.2% NaOH/0.01% SDS and protein determined using fluorescamine fluorescence. Stowell, C. P. *et al.*, *Anal. Biochem.*, 85, 572-580 (1978).

Saturation binding assays for human A_{2B} adenosine receptors were performed with [³H]ZM214,385 (17 Ci/mmol, Tocris Cookson, Bristol UK) (Ji, X. *et al.*, *Drug Design Discov.*, 16, 216-226 (1999)) or ¹²⁵I-ABOPX (2200 Ci/mmol). To prepare ¹²⁵I-ABOPX, 10 µL of 1 mM ABOPX in methanol/1 M NaOH (20:1) was added to 50 µL of 100 mM phosphate buffer, pH 7.3. One or 2 mCi of Na¹²⁵I was added, followed by 10 µL of 1 mg/mL chloramine-T in water. After incubation, 20 minutes at room temperature, 50 µL of 10 mg/mL Na-metabisulfite in water was added to quench the reaction. The reaction mixture was applied to a C18 HPLC column, eluting with a mixture of methanol and 5 mM phosphate, pH 6.0. After 5 min at 35% methanol, the methanol concentration was ramped to 100% over 15 min. Unreacted ABOPX eluted in 11-12 minutes; ¹²⁵I-ABOPX eluted at 18-19 min in a yield of 50-60% with respect to the initial ¹²⁵I.

In equilibrium binding assays the ratio of ¹²⁷I/¹²⁵I-ABOPX was 10-20/1. Radioligand binding experiments were performed in triplicate with 20-25 µg membrane protein in a total volume of 0.1 mL HE buffer supplemented with 1 U/mL adenosine deaminase and 5 mM MgCl₂. The incubation time was 3 h at 21°C. Nonspecific binding was measured in the presence of 100 µM NECA. Competition experiments were carried out using 0.6 nM ¹²⁵I-ABOPX. Membranes were filtered on Whatman GF/C filters using a Brandel cell harvester (Gaithersburg, MD) and washed 3 times over 15-20 seconds with ice cold buffer (10 mM Tris, 1 mM MgCl₂, pH 7.4). B_{max} and K_D values were calculated by Marquardt's nonlinear least squares interpolation for single a site

binding models. Marquardt, D. M., *J. Soc. Indust. Appl. Math.*, **11**, 431-441.21 (1963). K_i values for different compounds were derived from IC_{50} values as described. Linden, J., *J. Cycl. Nucl. Res.*, **8**, 163-172 (1982).

Data from replicate experiments are tabulated as means \pm SEM.

5

At other Adenosine Receptors:

- [³H]CPX. Bruns, R. F. *et al.*, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **335**, 59-63 (1987). ¹²⁵I-ZM241385 and ¹²⁵I-ABA were utilized in radioligand binding assays to membranes derived from HEK-293 cells expressing
- 10 recombinant human A₁, A_{2A} and A₃ ARs, respectively. Binding of [³H]R-N⁶-phenylisopropyladenosine. Schwabe, U. *et al.*, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **313**, 179-187 (1980). ([³H]R-PIA, Amersham, Chicago, IL) to A₁ receptors from rat cerebral cortical membranes and of [³H]CGS 21680. Jarvis, M.F. *et al.*, *J. Pharmacol. Exp. Therap.*, **251**, 888-893 (1989). (Dupont NEN,
- 15 Boston, MA) to A_{2A} receptors from rat striatal membranes was performed as described. Adenosine deaminase (3 units/mL) was present during the preparation of the brain membranes, in a pre-incubation of 30 min at 30°C, and during the incubation with the radioligands. All non-radioactive compounds were initially dissolved in DMSO, and diluted with buffer to the final
- 20 concentration, where the amount of DMSO never exceeded 2%. Incubations were terminated by rapid filtration over Whatman GF/B filters, using a Brandell cell harvester (Brandell, Gaithersburg, MD). The tubes were rinsed three times with 3 mL buffer each.

- At least six different concentrations of competitor, spanning 3 orders of
- 25 magnitude adjusted appropriately for the IC_{50} of each compound, were used. IC_{50} values, calculated with the nonlinear regression method implemented in (Graph-Pad Prism, San Diego, CA), were converted to apparent K_i values as described. Linden, J., *J. Cycl. Nucl. Res.*, **8**:163-172 (1982). Hill coefficients of the tested compounds were in the range of 0.8 to 1.1.

30

Functional assay:

HEK-A_{2B} cells from one confluent T75 flask were rinsed with Ca²⁺ and Mg²⁺-free Dulbecco's phosphate buffered saline (PBS) and then incubated in Ca²⁺ and Mg²⁺-free HBSS with 0.05% trypsin and 0.53 mM EDTA until the cells detached. The cells were rinsed twice by centrifugation at 250 x g in PBS and resuspended in 10 mL of HBSS composed of 137 mM NaCl, 5 mM KCl, 0.9 mM MgSO₄, 1.4 mM CaCl₂, 3 mM NaHCO₃, 0.6 mM Na₂HPO₄, 0.4 mM KH₂PO₄, 5.6 mM glucose, and 10 mM HEPES, pH 7.4 and the Ca²⁺-sensitive fluorescent dye indo-1-AM (5 μM) 37° for 60 min. The cells were rinsed once and resuspended in 25 mL dye-free HBSS supplemented with 1 U/ml adenosine deaminase and held at room temperature. Adenosine receptor antagonists prepared as 100X stocks in DMSO or vehicle was added and the cells and transferred to a 37° bath for 2 minutes. Then the cells (1 million in 2 ml) were transferred to a stirred cuvette maintained at 37° within an Aminco SLM 8000 spectrofluorometer (SML instruments, Urbana IL). The ratios of indo-1 fluorescence obtained at 400 and 485 nm (excitation, 332 nm) was recorded using a slit width of 4 nm. NECA was added after a 100 s equilibration period.

Cyclic AMP accumulation

Cyclic AMP generation was performed in DMEM/HEPES buffer (DMEM containing 50 mM HEPES, pH 7.4, 37°C). Each well of cells was washed twice with DMEM/HEPES buffer, and then 100 μL adenosine deaminase (final concentration 10 IU/mL) and 100 μL of solutions of rolipram and cilostamide (each at a final concentration of 10 μM) were added, followed by 50 μL of the test compound (appropriate concentration) or buffer. After 15 minutes, incubation at 37°C was terminated by removing the medium and adding 200 μL of 0.1 M HCl. Acid extracts were stored at -20°C until assay. The amounts of cyclic AMP were determined following a protocol which utilized a cAMP binding protein (PKA) [van der Wenden *et al.*, 1995], with the following minor modifications. The assay buffer consisted of 150 mM K₂HPO₄/10 mM EDTA/ 0.2% BSA FV at pH 7.5. Samples (20 mL) were incubated for 90 minutes at 0°C. Incubates were filtered over GF/C glass microfiber filters in a Brandel M-24 Cell Harvester. The filters were additionally rinsed with 4 times

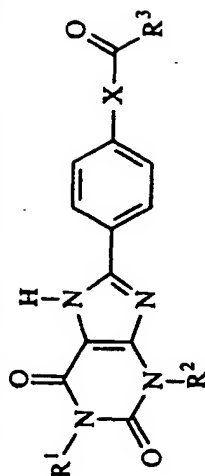
2 mL 150 mM K_2HPO_4 / 10 mM EDTA (pH 7.5, 4°C). Punched filters were counted in Packard Emulsifier Safe scintillation fluid after 2 hours of extraction.

The data from the affinity testing for the compounds of the invention are reported in Tables 1, 2, 3 and 4. The data are reported as K_i in nM or

- 5 % displacement of specific binding at the designated concentration (where "r" indicates rat cell receptors and "h" indicates human cell receptors).

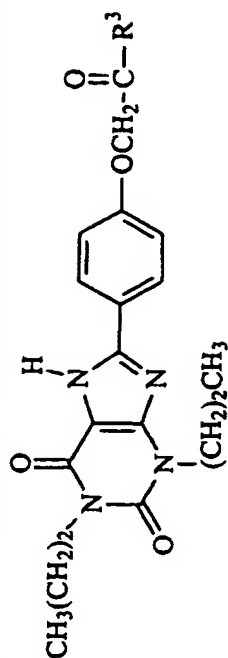
- The data reported for the A_1 term indicates the level of displacement of specific [3H]R-PIA binding in rat brain membranes (rA_1) or recombinant human A_1 receptors (hA_1) in HEK 293 cells, expressed as $K_i \pm$ S.E.M. ($n = 3-5$). The
- 10 data reported for the A_{2A} term is the level of displacement of specific [3H]CGS 21680 binding in rat striatal membranes (rA_{2A}) or recombinant human A_{2A} receptors (hA_{2A}) in HEK 293 cells, expressed as $K_i \pm$ S.E.M. ($n = 3-5$). The data reported for the A_{2B} term is the level of displacement of specific [^{125}I]ABOPX binding at human A_{2B} receptors (hA_{2B}) expressed in HEK-293 cells, expressed as
- 15 $K_i \pm$ S.E.M. ($n = 3-4$). The A_3 term is the level of displacement of specific [^{125}I]ABA binding at human A_3 receptors (hA_3) expressed in HEK-293 cells, in membranes, expressed as $K_i \pm$ S.E.M. ($n = 3-4$).

- In Table 4 the data reported for the A_{2A} term is the level of displacement of specific [3H]CGS 21680 binding to rat striatal membranes (rA_{2A}) or
- 20 [^{125}I]ABOPX binding to recombinant human A_{2B} receptors (hA_{2B}) in HEK 293 cells, expressed as $K_i \pm$ S.E.M. in μM ($n = 3-6$) or as a percentage of specific binding displaced by a solution of test compound, at the the designated concentration. In Table 4 the data reported for the hA_3 term is the level of displacement of specific [^{125}I]AB-MECA binding at human A_3 receptors
- 25 expressed in HEK-293 cells, in membranes, expressed as $K_i \pm$ S.E.M. in μM ($n = 3-4$).

Table 1. Affinities or antagonistic activities of xanthine derivatives in radioligand binding assays at A₁, A_{2A}, A_{2B} and A₃ receptors.

Compound	R ¹ , R ²	X	R ³	K _i or IC ₅₀ (nM)	rA ₁	rA _{2A}	hA _{2B}	hA ₁	hA ₁ /hA _{2B}	hA _{2A} /hA _{2B}	hA ₃ /hA _{2B}	hA ₃ /hA _{2A}
4a	n-Pr	OCH ₃	OH	58	175 ± 57(h)	2,200	40 ± 4	3,910 ± 2,140	4.4	15	98	
4b	n-Pr	OCH ₃	O-Succinimide	153	595 ± 128(h)	127	9.75 ± 4.80	75,700 ± 6,500(r)	227			
4c	n-Pr	OCH ₃	NHN-dimethylmaleyl	11.1 ± 2.4	3,030 ± 1,110(h)	126 ± 41	26.6 ± 4.0	670 ± 154	110	74	25	
4d	n-Pr	OCH ₃	NH(CH ₂) ₂ NH ₂	1.2	6.82 ± 1.57(h)	18.4 ± 0.03(h)	7.75 ± 0.14	25.6 ± 5.0	0.9	2.4	3.3	
5	allyl	OCH ₃	OH	756 ± 147	1,660 ± 580(h)	4,290 ± 570	141 ± 29(h)	816 ± 91	12	17	5.8	
6	n-butyl	OCH ₃	OH	43.1 ± 9.9	149 ± 83(h)	2,370 ± 290(h)	48.0 ± 16.9	173,000 ± 18,000(r)	3.1	53	1.9	
7	Bn	OCH ₃	OH	679 ± 190	25 ± 3% (100,000 nM) ^a	2,540 ± 1,250(h)	1,760 ± 110	90.3 ± 14.2				
8	n-Pr	CH=CH	OH	15	140 ± 3 (h)	800	60 ± 2	27,500 ± 2,500(r)	2.3	3.2	0.5	
9	c-HexylCH ₂	CH=CH	OH	602 ± 24	< 10% (10,000nM) ^a	190 ± 71 (h)	199 ± 52	15,000 ± 1,700(r)	25	7.6	4.6	
10	Bn	CH=CH	OH	4,890 ± 530(h)	201 ± 23	1,518 ± 980(h)	469 ± 23	922 ± 399				
71	CH-CH=CH ₂	OCH ₃	NH-Ph(4-CN)	61,200 ± 43,000	4,230 ± 340	9.53 ± 1.9	2680 ± 1810					

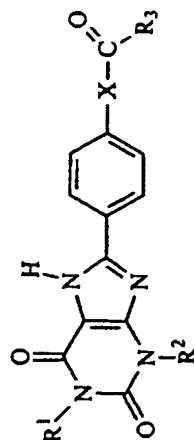
a) % Displacement of specific binding at the designated concentration of test compound.

Table 2. Affinities or antagonistic activities of xanthine amide derivatives in radioligand binding assays^a at A₁, A_{2A}, A_{2B} and A₃ receptors.

Compound	R ³	K _i or IC ₅₀ (nM)									
		rA ₁	rA _{2A}	hA ₁	hA _{2A}	hA _{2B}	hA ₃	hA ₁ /hA _{2B}	hA ₁ /hA ₃	hA _{2A} /hA _{2B}	
11	NH ₂	20.0 ± 3.8	76.3 ± 14.0			16.3 ± 4.2					
12	NH-Ph	4.22 ± 0.88	45.6 ± 1.4	40.1 ± 5.1	25.8 ± 4.5	1.48 ± 0.63	137 ± 54	27	17	93	
13	NH-CH ₂ Ph	5.02 ± 0.55	25.9 ± 7.6	54.7 ± 21.2	23.8 ± 5.71	2.04 ± 0.17	79.2 ± 17.8	27	12	39	
14	NH-CH(Ph) ₂	120 ± 21	20 ± 8% (1000) ^b			33.7 ± 17.0					
15	N(CH ₂ Ph) ₂	167 ± 49	2,750 ± 800	690 ± 98	642 ± 198	9.88 ± 1.05	284 ± 14	70	65	29	
16	N(CH ₃)Ph	218 ± 80	497 ± 250			5.42 ± 1.71					
17	N(CH ₂ COOEt) ₂	26.8 ± 2.4	299 ± 144			43.4 ± 8.4					
18	NH-Ph-(2-COCH ₃)	27.9 ± 1.6	434 ± 129	335 ± 64	431 ± 176	2.74 ± 1.01	61.9 ± 3.4	120	160	23	
19	NH-Ph-(3-COCH ₃)	439 ± 111	949 ± 394	234 ± 28	58.9 ± 7.1	4.92 ± 0.55	352 ± 69	48	12	72	
20	NH-Ph-(4-COCH ₃)	37.6 ± 4.0	548 ± 183	157 ± 8	112 ± 37	1.39 ± 0.30	230 ± 23	110	81	170	
21	NH-Ph-(4-COOCH ₃)	38.4 ± 3.9	541 ± 128	225 ± 9	3,100 ± 1540	3.93 ± 1.35	363 ± 148	57	790	92	
22	NH-Ph-(4-CONH ₂)	10.2 ± 2.5	683 ± 167			7.75 ± 1.11					
23	NH-Ph-(4-CONHCH ₃)	24.8 ± 1.8	98.1 ± 49.6			3.34 ± 0.51					
24	NH-Ph-(4-COOH)	145 ± 28	220 ± 79			16.1 ± 4.7					

Compound	R'	K _i or IC ₅₀ (nM)									
		rA ₁	rA _{2A}	hA ₁	hA _{2A}	hA _{2B}	hA ₁	hA ₁ /hA _{2B}	hA ₁ /hA _{2B}	hA _{2A} /hA _{2B}	
25	NH-Ph-(4-CH ₃)	17.5 ± 5.0	126 ± 38			1.88 ± 0.76					
26	NH-Ph-(4-OH)	5.88 ± 1.06	63.3 ± 20.4			3.71 ± 0.76					
27	NH-Ph-(4-CN)	16.8 ± 3.6	612 ± 287			1.97 ± 0.31					
28	NH-Ph-(4-NO ₂)	13.1 ± 3.9	1,180 ± 360			1.52 ± 0.24					
29	NH-Ph-(4-CF ₃)	44.6 ± 6.5	917 ± 258	403 ± 194	503 ± 10.8	1.97 ± 0.31	570 ± 184	210	260	290	
30	NH-Ph-(4-F)	2.72 ± 0.51	988 ± 518	57.0 ± 3.1	70.0 ± 10.7	1.52 ± 0.24	138 ± 17.1	38	46	91	
31	NH-Ph-(4-Cl)	6.35 ± 1.47	995 ± 550	61.2 ± 8.2	238 ± 28	2.14 ± 0.47	213 ± 94	29	110	100	
				17.9 ± 4.5	16.6 ± 3.6	2.22 ± 0.19	391 ± 147	8.1	7.5	176	
				49.7 ± 14.2	187 ± 38	2.47 ± 0.71	1,870 ± 370	20	400	760	
32	NH-Ph-(4-Br)	7.46 ± 2.66	221 ± 36	73.5 ± 23.3	1,640 ± 660	2.35 ± 0.01	2,300 ± 420	31	700	980	
33	NH-Ph-(4-I)	15.7 ± 4.2	152 ± 47	293 ± 67	5,140 ± 540	2.13 ± 0.12	1,270 ± 130	140	2,400	600	

a) The methods of each binding assay are described above.

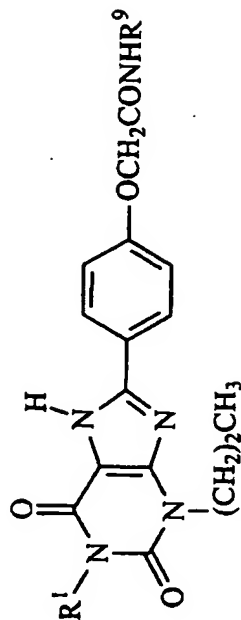
Table 3. Affinities or antagonistic activities of miscellaneous xanthine derivatives in radioligand binding assays^a at A₁, A_{2A}, A_{2B} and A₃ receptors.K_i or IC₅₀ (nM)

Compound	R ¹ , R ²	X	R ³	rA ₁	rA _{2A}	hA _{2B}	hA ₃
34	n-Pr	CH=CH	NH-Ph-(2-COCH ₃)	3.94 ± 1.20	406 ± 105	16.7 ± 3.0	31.0 ± 3.1
35	n-Pr	CH=CH	NH-Ph-(2-COCH ₃)	105 ± 5(h)	223 ± 55(h)		
				7.67 ± 2.20	143 ± 50	3.65 ± 0.98	121 ± 138
36	c- HexMe	CH=CH	NH-Ph-(2-COCH ₃)	(10,000 nM) ^b	(10,000 nM) ^b	(10,000 nM) ^b	
37	Bn	CH=CH	NH-Ph-(2-COCH ₃)	34,300	(10,000 nM) ^b	(10,000 nM) ^b	
38	Bn	OCH ₃	NH-Ph-(2-COCH ₃)	(10,000 nM) ^b	(10,000 nM) ^b	(10,000 nM) ^b	
39	Et	OCH ₃	NH-Ph-(4-CH ₃)	34.9 ± 0.3	71.1 ± 7.7	1.78 ± 0.43	(1000 nM) ^b
40	Et	OCH ₃	NH-Ph- (4-CH ₃ CONH- (CH ₂) ₂ NH ₂)	65.0 ± 15.4	1370 ± 490	15.2 ± 6.8	

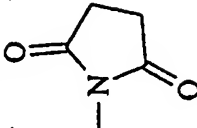
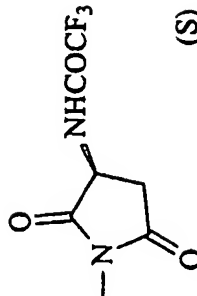
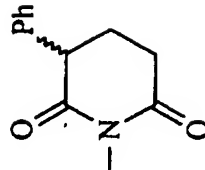
a) The methods of each binding assay are as described above.

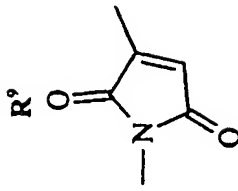
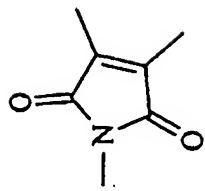
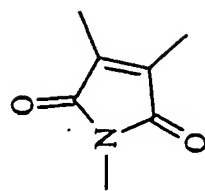
b) <10% displacement of specific binding at the designated concentration of test compound.

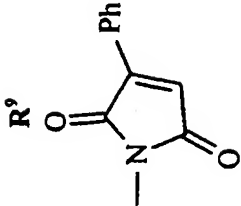
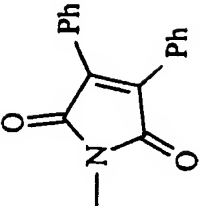
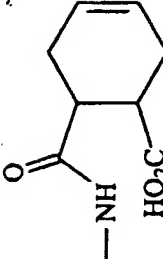
Table 4. Affinities of xanthine derivatives in radioligand binding assays^b at rat A₁, rat A_{2A}, human A_{2B}, and human A₃ receptors, unless noted^a.

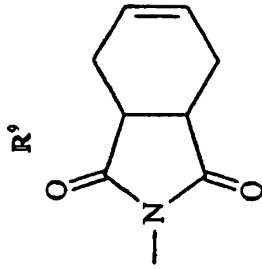
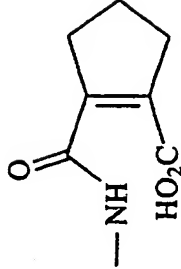
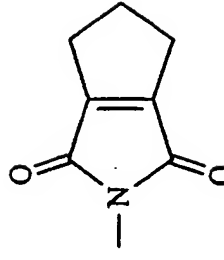


Compound	R ⁹	R ¹	K _i (nM) or % displacement				
			rA ₁	rA _{2A}	hA _{2B}	hA ₃	rA ₁ /hA _{2B}
4e	-	Pr	51.6 ± 8.0, 230 ± 59 (h) ^a	128 ± 15, 342 ± 10 (h) ^a	18.7 ± 0.5, 34.5 ± 6.3 ^a	48.5 ± 0.8 ^a	2.8
4f	-NH ₂	Pr	16.0 ± 0.5	63.8 ± 21.3	13.2 ± 5.9	498 ± 139	1.2
41	-NH-COCH ₃	Pr	6.51 ± 1.24, 125 ± 14 (h) ^a	227 ± 64, 186 ± 9 (h) ^a	65.4 ± 6.5, 33.8 ± 13.7 ^a	30.9 ± 8.2 ^a	0.10
42		Pr	73.3 ± 22.0, 219 ± 3 (h) ^a	174 ± 32, 795 ± 98 (h) ^a	116 ± 10, 97.8 ± 3.3 ^a	173 ± 27	1.6

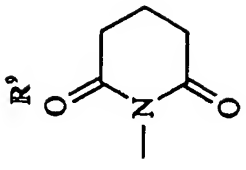
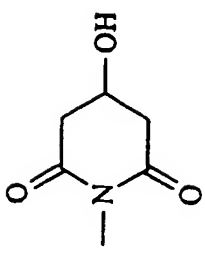
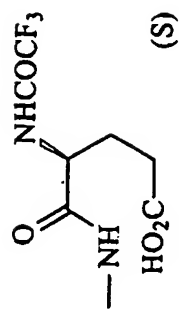
Compound	R ⁹	KI (nM) or % displacement				
		rA ₁	rA _{2A}	hA _{2B}	hA ₃	rA ₁ /hA _{2B}
43		55.9 ± 25.1	805 ± 44	18.6 ± 6.1	766 ± 176	3.0
		75.2 ± 5.5 (h) ^a	27.2 ± 8.6 (h) ^a			
44						
		74.3 ± 6.6	139 ± 32	30.2 ± 0.5	1560	2.5
45						
		3.87 ± 1.20	21.4 ± 6.1	3.86 ± 0.7	151 ± 99	1.0

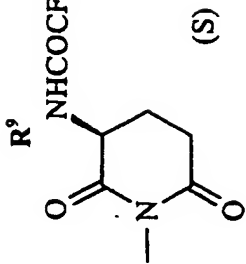
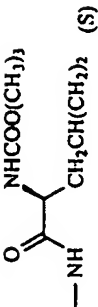
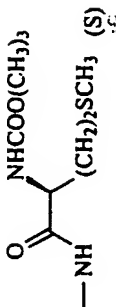
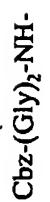
Compound	R'	R ²	KI (nM) or % displacement				
			rA ₁	rA _{2A}	hA _{2B}	hA ₃	rA ₁ /hA _{2B}
46	Pr		203 ± 41	1230 ± 270	144 ± 11	551 ± 106	1.4
47	Pr		11.1 ± 2.4, 3030 ± 1110 (h) ^a	126 ± 41, 1970 ± 550 (h) ^a	19.4 ± 6.2, 33.8 ± 1.9 ^a	670 ± 154 ^a	0.57
48	H		3590 ± 920, 8080 ± 720 (h) ^a	36 ± 4% (100,000 nM) ^c ; 5480 ± 920 (h) ^a	1800 ± 0, 1900 ± 280 ^a	14,200 ± 11,500 ^a	2.0

Compound	R'		Ki (nM) or % displacement				
			rA ₁	rA _{2A}	hA _{2B}	hA ₃	rA ₁ /hA _{2B}
49	Pr		225 ± 76	1540 ± 280	66.7 ± 37.0	748 ± 234	3.4
50	Pr		95.8 ± 25.1	2100 ± 630	27.9 ± 8.5	3450 ± 1470	3.4
51	Pr		134 ± 19	813 ± 299	51.0 ± 7.0	1060 ± 150	2.6

Compound	R'	R''	Ki (nM) or % displacement				
			rA ₁	rA _{1A}	hA _{2B}	hA ₃	rA ₁ /hA _{2B}
52	Pr		36.4 ± 6.2	689 ± 477	10.0 ± 3.0	370 ± 190	3.6
			129 ± 20 (h) ^a	301 ± 31 (h) ^a			
53	Pr		81.7 ± 31.2	708 ± 169	78.5 ± 20.5	1180 ± 700	1.0
54	Pr		41.3 ± 6.4	1160 ± 337	21.5 ± 1.5	309 ± 88	1.9

Compound	R ⁹	R ¹	KI (nM) or % displacement				
			rA ₁	rA _{2A}	hA _{2B}	hA ₃	rA ₁ /hA _{2B}
55		Pr	47.2 ± 6.8	422 ± 136	17.3 ± 6.3	438 ± 109	2.7
			145 ± 11 (h) ^a	95.6 ± 16.8 (h) ^a			
56		Pr	61.9 ± 11.3	415 ± 157	35.8 ± 0.7	245 ± 45	1.7
57		Pr	26.3 ± 2.3,	392 ± 117,	64.4 ± 0.8,	147 ± 21 ^a	0.41
			210 ± 42 (h) ^a	359 ± 21 (h) ^a	46.4 ± 14.5 ^a		

Compound	R ⁹	R ¹	KI (nM) or % displacement				
			rA ₁	rA _{2A}	hA _{2B}	hA ₃	rA ₁ /hA _{2B}
58		Pr	14.0 ± 2.3	135 ± 39	22.0 ± 5.5	200 ± 45	0.6
59		Pr	41.2 ± 16.6	164 ± 61	25.7 ± 5.5	290 ± 88	1.6
60		Pr	70.8 ± 30.9	872 ± 412	24.8 ± 7.3	430 ± 44	2.9

Compound	R ²	R ¹	K _i (nM) or % displacement				
			rA ₁	rA _{2A}	hA _{2B}	hA ₃	rA ₁ /hA _{2B}
61	 (S)	Pr	53.5 ± 6.5	440 ± 106	13.0 ± 3.5	726 ± 245	4.1
			149 ± 6 (h) ^a	178 ± 20 (h) ^a			
62	 (S)	Pr	197 ± 67	2750 ± 950	47.5 ± 2.5	195 ± 84	4.1
63	 (S)	Pr	113 ± 27	524 ± 285	39.7 ± 13.6	690 ± 570	2.8
64	 (S)	Pr	36.0 ± 6.6 200 ± 22 (h) ^a	609 ± 95 830 ± 84 (h) ^a	10.8 ± 5.0	323 ± 47	3.3

a) K_i values were determined in radioligand binding assays at recombinant human A₁ and A_{2A} receptors expressed in HEK-293 cells vs [³H]CPX and [¹²⁵I]ZM241385, respectively. Affinity of xanthine derivatives at human A_{2B} receptors expressed in HEK-293 cells was determined using [¹²⁵I]-ABOPX. Affinity at recombinant human A₃ receptors expressed in HEK-293 cells was determined using [¹²⁵I]ABA.

b) The methods of each binding assay are as described above.

c) % Displacement of specific binding at the the designated concentration of test compound.

The potency of the xanthine derivatives at human A_{2B} receptors was evaluated using two binding assays. Tables 1, 2 and 3 illustrate the results from the anilide compounds. Table 4 illustrates the results from the hydrazide compounds. Figure 2 shows functional inhibition by anilide compounds. The K_i values of the xanthine derivatives were determined in displacement of binding of two non-selective radioligands 4-(2-[7-amino-2-furyl]{1,2,4}triazolo[2,3-a]{1,3,5}triazin-5-ylaminoethyl)-phenol ($[^3H]$ ZM241385), and ^{125}I -3-(4-amino-3-iodobenzyl)-8-phenyloxyacetate-1-propyl-xanthine (^{125}I -ABOPX), at human A_{2B} receptors stably expressed in HEK-293 cell membranes. The results obtained with these two radioligands were nearly identical. In order to determine selectivity, the xanthines were evaluated using standard binding assays at A_1 , A_{2A} , and A_3 receptors. The initial screening utilized rat brain A_1/A_{2A} receptors (with radioligands $[^3H]$ R-PIA and $[^3H]$ CGS21680), and selected compounds were examined at the recombinant human subtypes, using $[^3H]$ 8-cyclopentyl-1,3-dipropylxanthine ($[^3H]$ CPX) (A_1 , See Bruns, R.F., *et al.*, *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1987, 335, 59-63.) and ^{125}I -4-(2-[7-amino-2-[2-furyl]-[1,2,4]triazolo[2,3-a][1,3,5]-triazin-5-yl-amino]-ethyl)phenol (^{125}I -ZM241385) (A_{2A}). Affinity at cloned human A_3 receptors expressed in HEK-293 cells was determined using N^6 -(4-amino-3- $[^{125}I]$ iodobenzyl)-adenosine (^{125}I -ABA) or N^6 -(4-amino-3-iodobenzyl)-adenosine-5'-*N*-methyluronamide (^{125}I -AB-MECA).

The 8-(4-Phenylacrylic) acid derivatives, 8 - 10, tended to be more potent at A_1 receptors and less potent at A_{2B} receptors than the 8-(4-carboxymethoxyphenyl) derivatives. The 1,3-dicyclohexylmethyl derivative, 9, for example, was more selective for A_{2B} receptors. A primary carboxamide, 11, was more potent than the carboxylic acid, 4a, at A_1 (3-fold) and A_{2A} (29-fold) receptors, and equipotent at A_{2B} receptors.

The adenosine receptor affinities of aryl, compounds 12 and 18 - 33, alkyl, compound 17, and aralkyl, compounds 13 - 16, amides of 4a were compared. A benzyl amide, compound 13, and simple anilides had the highest affinity of binding, in the nanomolar range, to human A_{2B} receptors. Selectivities for the human A_{2B} versus rat A_1 receptors ranged from 1- (compound 30) to 27- (compound 20) fold, while comparisons within the same species (human)

generally led to greater selectivities. Anilides substituted in the *p*-position with groups such as nitro, cyano, and acetyl, displayed the highest selectivity. An N-methyl anilide of 4a, compound 16, was 40- and 92-fold selective for human A_{2B} receptors versus rat A₁/A_{2A} receptors, thus the N-methylation reduced
5 affinity by 3.7-fold but increased selectivity. An *o*-substituted acetophenone, compound 18 was 120-, 160-, and 23-fold selective for human A_{2B} receptors versus human A₁/A_{2A}/A₃ receptors and 10-, and 160-fold selective versus rat A₁/A_{2A} receptors. The *p*-substituted acetophenone, compound 20, was more potent at A_{2B} receptors than the corresponding *o*- and *m*- isomers. Other
10 highly potent and moderately selective A_{2B} antagonists were a *p*-trifluoromethyl derivative, compound 29 (K_i value 2.14 nM), and a *p*-cyanoanilide, compound 27 (K_i value 1.97 nM), which was highly selective versus the other human subtypes, but only 8.5-fold selective versus rat A₁ receptors. The *p*-cyanoanilide, 27, was tritiated on the 1,3-dipropyl groups and
15 serves as a selective radio ligand for A_{2B} receptors. A *p*-nitro derivative, compound 28, bound to human A_{2B} receptors with a K_i of 1.52 nM but was only 35-fold selective versus human A₁ receptors. A *p*-iodo derivative, compound 33 (K_i value 2.13 nM), was 140-, 2400-, and 600-fold selective for human A_{2B} receptors versus human A₁/A_{2A}/A₃ receptors. Substitution of the
20 1,3-dipropyl groups with ethyl, as in compounds 40 and 41, offered no disadvantage for selectivity, but high affinities were maintained.

The functional effects of several selective A_{2B} antagonists in inhibiting the effects of NECA in HEK-A_{2B} cells were examined (Figure 2). Several selective A_{2B} adenosine receptor antagonists at 100 nM nearly completely
25 inhibited NECA-stimulated calcium mobilization. In comparison, XAC (8-[4-[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine), which has a K_i value of 12.3 nM in binding to human A_{2B}, (See de Zwart, M.; *et al.*, *Nucleos. Nucleot.* 1998, 17, 969-986.) inhibited the NECA-stimulated calcium mobilization effect by about half. Thus, the potency of the xanthines
30 in the functional assay was parallel to results from the binding assay.

The 1,2-dimethylmaleimide derivative, 47, bound to human A_{2B} receptors with a K_i of 19 nM and proved to be selective vs. human A₁/A_{2A}/A₃ receptors by 160-, 100-, and 35-fold, respectively. Other potent and selective A_{2B}

antagonists were a tetrahydrophthaloyl derivative 52 (K_i value 10 nM) and amino acid conjugates of the XCC-hydrazide, *i.e.*, the glutarimide 61 (K_i value 13 nM) and protected dipeptide 64 (K_i value 11 nM). Compound 55 displayed a K_i value of 17 nM. Other derivatives displaying selectivity for A_{2B} receptors, but with less potency (K_i values in nM) were compounds: 44 (30), 49 (67), 50 (28), 60 (25), 62 (48), and 63 (40).

Synthesis and Characterization

Compounds 4a, 4b, 4c, 11, 25, and 26 were synthesized as reported in Jacobson, *et al.*, *J. Med. Chem.* 1985, 28, 1334-1340. Compound 5, 6, 7 and 10 were synthesized as reported in Kim, H. O.; *et al.*, *J. Med. Chem.* 1994, 37, 3373-3382. Compound 39 and 40 were synthesized as reported in Jacobson, K. A *et al.*, *J. Med. Chem.* 1987, 30, 211-214. *R*-PIA, NECA, XAC, and 2-chloroadenosine were purchased from Research Biochemicals International (Natick, MA). All other agents were purchased from Aldrich (St. Louis, MO).

Proton nuclear magnetic resonance spectroscopy was performed on a Varian GEMINI-300 spectrometer and spectra were taken in DMSO- d_6 or $CDCl_3$. Unless noted, chemical shifts are expressed as ppm downfield from tetramethylsilane or relative ppm from DMSO (2.5 ppm). Chemical-ionization (CI) mass spectrometry was performed with a Finnigan 4600 mass spectrometer, and Electron-impact (EI) mass spectrometry with a VG7070F mass spectrometer at 6 kV for high resolution mass. FAB (fast atom bombardment) mass spectrometry was performed with a JEOL SX102 spectrometer using 6-kV Xe atoms.

Elemental analysis ($\pm 0.4\%$ acceptable) was performed by Atlantic Microlab Inc. (Norcross, GA). All melting points were determined with a Unimelt capillary melting point apparatus (Arthur H. Thomas Co., PA) and were uncorrected. All xanthine derivatives were homogeneous as judged using TLC (MK6F silica, 0.25 mm, glass backed, Whatman Inc., Clifton, NJ). All xanthine derivatives tested in binding assays were shown to be homogeneous by TLC (MK6F silica, 0.25 mm, glass backed, Whatman Inc., Clifton, NJ). NMR and mass spectra were shown to be consistent with the assigned structure.

Example 1. General procedure for the preparation of amide derivatives of 8-[4-[[[carboxyl]methyl]oxy]phenyl]-1,3-dipropylxanthine analogs 4a, 7-10 (collectively "XCC")

Method A (Carbodiimide)

- 5 A solution of XCC (0.0517 mmole), the desired amine compound (0.103 mmole), EDAC (20 mg, 0.103 mmole), and DMAP (4 mg, 0.032 mmole) in 2 mL of anhydrous DMF/CH₂Cl₂ (1:1 v/v) was stirred at room temperature for 24 hours. The mixture was evaporated to dryness under reduced pressure. The residue was purified by preparative silica gel TLC
10 (CHCl₃:MeOH=20:1) and crystallization in MeOH/ether or MeOH/CH₂Cl₂ to afford the desired compounds (12-14, 18, 36).

Method B (BOP-Cl)

- A solution of XCC (0.0517 mmole), the desired amine compound
15 (0.103 mmole), BOP-Cl (14 mg, 0.0517 mmole), and triethylamine (20 μ l, 0.206 mmole) in 2 mL of anhydrous CH₂Cl₂ was stirred at room temperature for 24 hours. The mixture was treated according to the same procedure as Method A for purification of the desired compounds. (15, 17, 19, 20, 38)

20 **Method C (Acid Chloride)**

- A solution of XCC (0.0517 mmole) in 1 mL of thionyl chloride was stirred at 70°C for 4 hours. The excess thionyl chloride was removed with a nitrogen stream. To the residue was added a solution of the desired amine compound (0.103 mmole) in 1 mL of anhydrous pyridine and 1 mL of
25 anhydrous CH₂Cl₂. The mixture was stirred at room temperature for 24 hours. The mixture was subjected to the same procedure as described in Method A for purification of the desired compounds. (16, 21, 22, 27-35, 37)

Example 2. General procedure for the preparation of xanthine hydrazide derivatives

The hydrazide of XCC, 4f, was acylated with a variety of mono- and dicarboxylic acids. Cyclization reactions were carried out for dicarboxylic acids, in two steps using an anhydride, (compound 72, Figure 4), for acylation, leading to imide (5- or 6-membered ring) derivatives. The final step of ring-closure of 73 to 74 was effected at 50 °C, using excess carbodiimide and 1-hydroxybenzotriazole as catalyst. In some cases, where symmetric dicarboxylic acids were used, it was possible to isolate both the open structure, 73, and the cyclized imide form, 74. Pairs of open and cyclized derivatives of symmetric dicarboxylic acids prepared include compounds 51 - 56. Also, the glutamic acid derivative 60, was prepared using orthogonal protecting and the corresponding imide, 61. An 8-phenyl analogue, 48, of enprofylline was synthesized by standard methods from the asymmetric urea, (Figure 5).

A. Carboxyalkyl amide derivatives

A mixture of compound 4f (10 mg, 0.025 mmol), and 2 equivalents of anhydride were stirred in 1 mL of DMF for 6-24 hours. The reaction mixture was concentrated to dryness, and the residue was purified on preparative TLC (CHCl₃:MeOH=10:1) to afford the corresponding carboxyalkylamide derivative as a white solid with 40-70% yield. (compounds 41, 42, 51, 53, 55)

B. Cyclic imide derivatives

A mixture of compound 4f (10 mg, 0.025 mmol), 1.5-2.0 equivalents of anhydride and 1 equivalent of DIPEA were stirred in 1 mL of DMF at room temperature. When the starting material 4f disappeared, as judged by TLC, a mixture of 2-3 equivalents of HOBt, EDAC, and DIPEA, dissolved in 0.5 mL of DMF, was added. The mixture was stirred at room temperature or at 50°C for 6-24 hours. The reaction mixture was concentrated to dryness, and the residue was purified on preparative TLC (CHCl₃:MeOH=10:1) to afford the cyclic imide derivative as a white solid, 40-70% yield. (compounds 43, 44, 45, 46, 47, 48, 49, 50, 52, 54, 56, 57, 58, and 59)

C. Coupling with activated N-protected amino acids

A mixture of compound 4f (10 mg, 0.025 mmol), 1.5-2.0 equivalents of activated (hydroxy- succinimide or 4-nitrophenyl ester) N-protected amino acid and 1 equivalent of DIPEA and DMAP, in 1 mL of DMF, was stirred at 25-50°C for 8-24 hours. The reaction mixture was concentrated to dryness. The residue was purified by preparative TLC (CHCl₃:MeOH=10:1) to afford the product as a white solid, 40-70% yield. (compounds 62, 63 and 64)

Example 3. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-dibenzyl-xanthine (7)

¹H NMR (DMSO-d₆) 4.23 (s, 2H, -OCH₂-), 5.10 (s, 2H, -NCH₂-), 5.23 (s, 2H, -NCH₂-), 6.88 (d, 2H, *J* = 8.8 Hz, Ar), 7.22-7.41 (m, 10H, 2x-Ph), 8.01 (d, 2H, *J* = 8.8 Hz, Ar).

Example 4. 8-(4-(2-Carboxy-*trans*-vinyl)phenyl)-1,3-dibenzyl-xanthine

(10)

¹H NMR (DMSO-d₆) 5.12 (s, 2H, -NCH₂-), 5.26 (s, 2H, -NCH₂-), 6.63 (d, 1H, *J* = 15.6 Hz, -CH=), 7.22-7.43 (m, 10H, 2x-Ph), 7.63 (d, 1H, *J* = 15.6 Hz, -CH=), 7.84 (d, 2H, *J* = 8.8 Hz, Ar), 8.17 (d, 2H, *J* = 8.8 Hz, Ar).

Example 5. 8-[4-[(Phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)-xanthine (12)

¹H NMR (DMSO-d₆) 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.80 (s, 2H, -OCH₂-), 7.06-7.12 (m, 1H, -Ph), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.33 (t, 2H, *J* = 7.8 Hz, -Ph), 7.64 (d, 2H, *J* = 7.8 Hz, -Ph), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 10.13 (s, 1H, -NH).

Example 6. 8-[4-[(Benzylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)-xanthine (13)

¹H NMR (DMSO-d₆) 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.36 (d, 2H, *J* = 5.9 Hz, -NH-CH₂-), 4.80 (s, 2H, -OCH₂-), 7.12 (d, 2H, *J* = 8.8 Hz, Ar),

7.22-7.34 (m, 5H, -Ph), 8.08 (d, 2H, $J = 8.8$ Hz, Ar), 8.70 (t, 1H, $J = 5.9$ Hz, -NH-).

Example 7. 8-[4-[(Diphenylmethylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (14)

^1H NMR (DMSO- d_6). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.73 (s, 2H, -OCH₂-), 6.20 (d, 1H, $J = 8.8$ Hz, -NH-CH₂-), 7.08 (d, 2H, $J = 8.8$ Hz, Ar), 7.23-7.37 (m, 10H, 2x-Ph), 8.07 (d, 2H, $J = 8.8$ Hz, Ar), 9.06 (d, 1H, $J = 8.8$ Hz, -NH-).

Example 8. 8-[4-[(Dibenzylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (15)

^1H NMR (DMSO- d_6). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.52 (s, 2H, -NCH₂-), 4.59 (s, 2H, -NCH₂-), 5.03 (s, 2H, -OCH₂-), 6.99 (d, 2H, $J = 8.8$ Hz, Ar), 7.22-7.44 (m, 10H, 2x-Ph), 8.05 (d, 2H, $J = 8.8$ Hz, Ar).

Example 9. 8-[4-[(N-Methyl-N-phenylcarbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (16)

^1H NMR (DMSO- d_6). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.22 (s, 3H, -NCH₃), 3.88 and 4.01 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.54 (s, 2H, -OCH₂-), 6.91 (bs, 2H, Ar), 7.30-7.55 (m, 5H, -Ph), 8.03 (d, 2H, $J = 8.8$ Hz, Ar).

Example 10. 8-[4-[(N,N-bis(ethoxycarbonylmethyl)carbamoylmethyl)oxy]phenyl]-1,3-di-(n-propyl)xanthine (17)

^1H NMR (DMSO- d_6). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.20 (2t, 6H, $J = 6.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.06-4.20 (m, 4H, -OCH₂-), 4.11 (s, 2H, -NCH₂-), 4.38 (s, 2H, -NCH₂-), 4.94 (s, 2H, -OCH₂-), 7.00 (d, 2H, $J = 8.8$ Hz, Ar), 8.05 (d, 2H, $J = 8.8$ Hz, Ar).

Example 11. 8-[4-(((2-Acetylphenyl)carbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (18)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.70 (s, 3H, -COCH₃), 4.72 (s, 2H, -OCH₂-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 7.56 (t, 1H, *J* = 6.8 Hz, Ar), 7.69 (t, 1H, *J* = 6.8 Hz, Ar), 8.02 (d, 2H, *J* = 6.8 Hz, Ar), 8.11 (d, 2H, *J* = 8.8 Hz, Ar), 8.48 (m, 1H, -NH-).

Example 12. 8-[4-(((3-Acetylphenyl)carbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (19)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.74 (2m, 4H, 2x-CH₂-), 2.57 (s, 3H, -COCH₃), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.82 (s, 2H, -OCH₂-), 7.16 (d, 2H, *J* = 8.8 Hz, Ar), 7.50 (t, 1H, *J* = 7.8 Hz, Ar), 7.71 (d, 1H, *J* = 7.8 Hz, Ar), 7.92 (d, 1H, *J* = 7.8 Hz, Ar), 8.10 (d, 2H, *J* = 8.8 Hz, Ar), 8.24 (s, 1H, Ar), 10.36 (s, 1H, -NH-).

Example 13. 8-[4-(((4-Acetylphenyl)carbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (20)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 2.54 (s, 3H, -COCH₃), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.85 (s, 2H, -OCH₂-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 7.79 (d, 2H, *J* = 7.8 Hz, Ar), 7.96 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 10.48 (s, 1H, -NH-).

Example 14. 8-[4-(((4-Methoxycarbonyl)phenyl)carbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (21)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.83 (s, 3H, -OCH₃), 3.86 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.85 (s, 2H, -OCH₂-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.79 (d, 2H, *J* = 7.8 Hz, Ar), 7.96 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 10.50 (s, 1H, -NH-).

Example 15. 8-[4-(((4-Carbamoyl)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (22)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.82 (s, 2H, -OCH₂-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.26 (bs, 1H, -NH₂), 7.70 (d, 2H, *J* = 7.8 Hz, Ar), 7.85 (m, 3H, Ar and -NH₂), 8.10 (d, 2H, *J* = 8.8 Hz, Ar), 10.35 (s, 1H, -NH-).

Example 16. 8-[4-(((4-Methylcarbamoyl)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (23)

A solution of 20 mg of compound 21 (0.0358 mmole) in 1 mL of 40% aqueous methylamine was stirred at room temperature for 1 hour. The mixture was evaporated to dryness under reduced pressure, and the residue was purified by preparative silica gel TLC (CHCl₃:MeOH=20:1) and re-crystallized in MeOH/CH₂Cl₂ to afford 9 mg of compound 23. ¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.73 (2m, 4H, 2x-CH₂-), 2.76 (s, 3H, -NHCH₃), 3.86 and 4.01 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.82 (s, 2H, -OCH₂-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.71 (d, 2H, *J* = 7.8 Hz, Ar), 7.81 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 8.33 (m, 1H, -NHCH₃), 10.34 (s, 1H, -NH-).

Example 17. 8-[4-(((4-Carboxy)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (24)

A suspension of 20 mg of compound 21 (0.0385 mmole) in 1 mL of 1 N NaOH solution was stirred for 2 hours to turn to a clear solution. The mixture was neutralized by adding 1 mL of 1 N HCl solution. The precipitate was collected by filtration, and purified by low pressure (C18) column chromatography using linear gradient elution of 1 M triethylammonium acetate buffer (pH=7.0) and CH₃CN (90/10 to 40/60) to afford 10 mg of compound 24. ¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.01 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.84 (s, 2H, -

OCH₂-), 7.14 (d, 2H, $J = 8.8$ Hz, Ar), 7.77 (d, 2H, $J = 8.8$ Hz, Ar), 7.92 (d, 2H, $J = 8.8$ Hz, Ar), 8.09 (d, 2H, $J = 8.8$ Hz, Ar), 10.45 (s, 1H, -NH-).

Example 18. 8-[4-(((4-Cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (27)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.86 and 4.01 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.85 (s, 2H, -OCH₂-), 7.13 (d, 2H, $J = 8.8$ Hz, Ar), 7.80 (d, 2H, $J = 7.8$ Hz, Ar), 7.84 (d, 2H, $J = 7.8$ Hz, Ar), 8.09 (d, 2H, $J = 8.8$ Hz, Ar), 10.58 (s, 1H, -NH-).

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Example 19. 8-[4-(((4-Nitro)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (28)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.89 (s, 2H, -OCH₂-), 7.15 (d, 2H, $J = 8.8$ Hz, Ar), 7.91 (d, 2H, $J = 8.8$ Hz, Ar), 8.10 (d, 2H, $J = 8.8$ Hz, Ar), 8.26 (d, 2H, $J = 8.8$ Hz, Ar), 10.76 (s, 1H, -NH-).

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Example 20. 8-[4-(((4-Trifluoromethyl)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (29)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.85 (s, 2H, -OCH₂-), 7.15 (d, 2H, $J = 8.8$ Hz, Ar), 7.71 (d, 2H, $J = 7.8$ Hz, Ar), 7.87 (d, 2H, $J = 7.8$ Hz, Ar), 8.09 (d, 2H, $J = 8.8$ Hz, Ar), 10.51 (s, 1H, -NH-).

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Example 21. 8-[4-(((4-Fluoro)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (30)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.79 (s, 2H, -OCH₂-), 7.15 (d, 2H, $J = 8.8$ Hz, Ar), 7.19 (d, 2H, $J = 8.8$ Hz, Ar), 7.66 (dd, 2H, $J = 5.9, 8.8$ Hz, Ar), 8.10 (d, 2H, $J = 8.8$ Hz, Ar), 10.20 (s, 1H, -NH-).

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Example 22. 8-[4-(((4-Chloro)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (31)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.80 (s, 2H, -OCH₂-), 7.14 (d, 2H, *J* = 7.8 Hz, Ar), 7.39 (d, 2H, *J* = 7.8 Hz, Ar), 7.68 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 7.8 Hz, Ar), 10.27 (s, 1H, -NH-).

Example 23. 8-[4-(((4-Bromo)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (32)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.80 (s, 2H, -OCH₂-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.52 (d, 2H, *J* = 8.8 Hz, Ar), 7.63 (d, 2H, *J* = 8.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 10.27 (s, 1H, -NH-).

Example 24. 8-[4-(((4-Iodo)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (33)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.79 (s, 2H, -OCH₂-), 7.14 (d, 2H, *J* = 7.8 Hz, Ar), 7.49 (d, 2H, *J* = 7.8 Hz, Ar), 7.68 (d, 2H, *J* = 7.8 Hz, Ar), 8.09 (d, 2H, *J* = 7.8 Hz, Ar), 10.24 (s, 1H, -NH-).

Example 25. 8-(4-(2-Carboxy-*trans*-vinyl)phenyl)-1,3-di-(n-propyl)xanthine N',N'-[(1,2-Dimethyl)maleyl]hydrazide (34)

¹H NMR (CDCl₃). 1.01 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.72 and 1.89 (2m, 4H, 2x-CH₂-), 2.05 (s, 6H, 2x-CH₃), 4.02 and 4.17 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 6.67 (d, 1H, *J* = 15.6 Hz, -CH=), 7.63 (d, 2H, *J* = 8.8 Hz, Ar), 7.74 (d, 1H, *J* = 15.6 Hz, -CH=), 8.09 (d, 2H, *J* = 8.8 Hz, Ar), 9.43 (s, 1H, -NH-).

Example 26. 8-[4-(2-(2-Acetylphenyl)carbamoyl-*trans*-vinyl)phenyl]-1,3-di-(n-propyl)xanthine (35)

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.76 (2m, 4H, 2x-CH₂-), 3.88 and 4.04 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.79 (d, 3H, *J* = 4.9 Hz, -COCH₃), 6.93 (d, 1H, *J* = 15.6 Hz, -CH=), 7.51 (d, 1H, *J* = 15.6

Hz, -CH=), 7.57 (t, 1H, $J = 7.8$ Hz, Ar), 7.69 (t, 1H, $J = 7.8$ Hz, Ar), 7.75 (d, 2H, $J = 7.8$ Hz, Ar), 8.03 (d, 2H, $J = 7.8$ Hz, Ar), 8.18 (d, 2H, $J = 7.8$ Hz, Ar), 8.53 (t, 1H, $J = 5.8$ Hz, -NH-).

5 **Example 27. 8-[4-(2-(2-Acetylphenyl)carbamoyl-*trans*-vinyl)phenyl]-1,3-di-(cyclohexylmethyl)xanthine (36)**

^1H NMR (CDCl_3). 1.02-1.27 (m, 8H, c-Hex.), 1.45-1.72 (m, 14H, c-Hex.), 4.00 and 4.08 (2d, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.96 (d, 3H, $J = 3.9$ Hz, -COCH₃), 6.66 (d, 1H, $J = 15.6$ Hz, -CH=), 6.86 (bs, 1H, -NH-), 7.54 (t, 2H, $J = 7.8$ Hz, Ar), 7.64-7.78 (m, 3H, -CH= and Ar), 8.06 (d, 2H, $J = 7.8$ Hz, Ar), 8.24 (d, 2H, $J = 8.8$ Hz, Ar).

Example 28. 8-[4-(2-(2-Acetylphenyl)carbamoyl-*trans*-vinyl)phenyl]-1,3-dibenzylxanthine (37)

15 ^1H NMR ($\text{DMSO}-d_6$) 4.79 (d, 3H, $J = 5.8$ Hz, -COCH₃), 5.13 (s, 2H, -NCH₂-), 5.27 (s, 2H, -NCH₂-), 6.93 (d, 1H, $J = 15.6$ Hz, -CH=), 7.24-7.41 (m, 10H, 2x-Ph), 7.46 (d, 1H, $J = 15.6$ Hz, -CH=), 7.57 (t, 1H, $J = 8.8$ Hz, Ar), 7.69 (t, 1H, $J = 7.8$ Hz, Ar), 7.75 (d, 2H, $J = 8.8$ Hz, Ar), 8.03 (d, 2H, $J = 7.8$ Hz, Ar), 8.20 (d, 2H, $J = 7.8$ Hz, Ar), 8.54 (t, 1H, $J = 5.8$ Hz, -NH-).

20 **Example 29. 8-[4-[(2-Acetylphenyl)carbamoylmethyl]oxy]phenyl]-1,3-dibenzyl-xanthine (38)**

^1H NMR ($\text{DMSO}-d_6$) 4.68 (s, 3H, -COCH₃), 4.71 (s, 2H, -OCH₂-), 5.12 (s, 2H, -NCH₂-), 5.26 (s, 2H, -NCH₂-), 7.15 (d, 2H, $J = 8.8$ Hz, Ar), 7.23-7.42 (m, 10H, 2x-Ph), 7.55 (t, 1H, $J = 7.8$ Hz, Ar), 7.68 (t, 1H, $J = 7.8$ Hz, Ar), 8.02 (d, 2H, $J = 7.8$ Hz, Ar), 8.11 (d, 2H, $J = 8.8$ Hz, Ar), 8.48 (t, 1H, $J = 4.8$ Hz, -NH-).

30 **Example 30. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine *N*-Acetylhydrazide (41)**

^1H NMR ($\text{DMSO}-d_6$). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 1.88 (s, 3H, CH₃CO-), 3.87 and 4.02 (2t, 4H, $J = 6.8$ Hz,

2x-NCH₂-), 4.68 (s, 2H, -OCH₂-), 7.11 (d, 2H, *J* = 8.8 Hz, Ar), 8.08 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 443.

Example 31. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
***N*-[(3-Carboxy)-*n*-propionyl]hydrazide (42)**

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 2.43 (m, 4H, -COCH₂CH₂CO-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.67 (s, 2H, -OCH₂-), 7.11 (d, 2H, *J* = 8.8 Hz, Ar), 8.08 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 501.

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Example 32. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
***N,N*-Succinylhydrazide (43)**

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.73 (2m, 4H, 2x-CH₂-), 2.81 (s, 4H, CH₂CH₂), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.85 (s, 2H, -OCH₂-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.10 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 483.

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Example 33. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
***N,N*-[(2*S*)-Trifluoroacetamido]succinylhydrazide (44)**

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 2.70-2.90 (m, 2H, -CH₂-), 3.81 and 3.98 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.69 (s, 2H, -OCH₂-), 4.95 (s, 1H, -CH-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.10 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 594.

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Example 34. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
***N,N*-[(2-Phenyl)glutaryl]hydrazide (45)**

¹H NMR (CDCl₃). 1.05 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.75 and 1.90 (2m, 4H, 2x-CH₂-), 2.3-2.5 and 2.8-3.1 (m, 5H, -CH- and 2x-CH₂-), 4.04 and 4.12 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.70-4.90 (m, 2H, -OCH₂-), 6.6 (d, 2H, *J* = 8.8 Hz, Ar), 7.08 (m, 2H, -Ph), 7.43 (m, 5H, -Ph and Ar); MS-FAB (*M* + *H*⁺) 573.

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**Example 35. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N,N-Citraconylhydrazide (46)**

¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.73
(2m, 4H, 2x-CH₂-), 2.07 (s, 3H, CH₃), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz, 2x-
5 NCH₂-), 4.86 (s, 2H, -OCH₂-), 6.83 (s, 1H, =CH-), 7.15 (d, 2H, *J* = 8.8 Hz,
Ar), 8.10 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 495.

**Example 36. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N,N-[(1,2-Dimethyl)maleyl]hydrazide (47)**

10 ¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74
(2m, 4H, 2x-CH₂-), 1.97 (s, 6H, 2x-CH₃), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz,
2x-NCH₂-), 4.86 (s, 2H, -OCH₂-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 8.10 (d, 2H, *J* =
8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 509.

15 **Example 37. 8-[4-[(Carboxymethyl)oxy]phenyl]-1*H*-3-(*n*-propyl)xanthine
N,N-[(1,2-Dimethyl)maleyl]hydrazide (48)**

¹H NMR (DMSO-*d*₆). 0.91 (t, 3H, *J* = 7.8 Hz, 2x-CH₃), 1.73 (m, 2H,
-CH₂-), 1.97 (s, 6H, 2x-CH₃), 3.96 (t, 2H, *J* = 6.8 Hz, 2x-NCH₂-), 4.85 (s, 2H,
-OCH₂-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar); MS-EI
20 (*M*⁺) 509, Calcd. for C₂₂H₂₂N₆O₆ 466.1601; Found 466.1580.

**Example 38. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N,N-[(2-Phenyl)maleyl]hydrazide (49)**

¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.73
25 (2m, 4H, 2x-CH₂-), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.91 (s, 2H,
-OCH₂-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 7.51 (s, 1H, =CH-), 7.55-7.57 (m, 3H, -
Ph), 8.04-8.06 (m, 2H, -Ph), 8.11 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺)
557.

30 **Example 39. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N,N-[(1,2-Diphenyl)maleyl]hydrazide (50)**

¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.73
(2m, 4H, 2x-CH₂-), 3.87 and 4.03 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.94 (s, 2H,

-OCH₂-), 7.15 (d, 2H, $J = 8.8$ Hz, Ar), 7.45 (bs, 10H, 2x-Ph), 8.10 (d, 2H, $J = 8.8$ Hz, Ar); MS-FAB ($M + H^+$) 633.

Example 40. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
***N*-[2-[(1-Carboxy)-cis-4-cyclohexene)-carbonyl]hydrazide (51)**

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 2.30-2.50 (m, 4H, 2x-CH₂-), 2.80-2.95 (m, 2H, 2x-CH-), 3.83 and 3.90 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.66 (s, 2H, -OCH₂-), 5.63 (s, 2H, 2 x =CH-), 7.09 (d, 2H, $J = 8.8$ Hz, Ar), 8.06 (d, 2H, $J = 8.8$ Hz, Ar); MS-FAB ($M + H^+$) 553.

Example 41. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
***N,N*-(cis-1,2,3,6-Tetrahydrophthaloyl)hydrazide (52)**

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 2.20-2.50 (m, 4H, 2x-CH₂-), 3.56 (m, 2H, 2x-CH-), 3.83 and 3.90 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.66 (s, 2H, -OCH₂-), 5.89 (s, 2H, 2 x =CH-), 7.09 (d, 2H, $J = 8.8$ Hz, Ar), 8.06 (d, 2H, $J = 8.8$ Hz, Ar); MS-FAB ($M + H^+$) 535.

Example 42. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
***N*-[2-[(1-Carboxy)-1-cyclopentene)-carbonyl]hydrazide (53)**

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 1.87 (m, 2H, -CH₂-), 2.70 (m, 4H, 2x-CH₂-), 3.83 and 3.90 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.71 (s, 2H, -OCH₂-), 7.09 (d, 2H, $J = 8.8$ Hz, Ar), 8.06 (d, 2H, $J = 8.8$ Hz, Ar); MS-FAB ($M + H^+$) 539.

Example 43. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
***N,N*-(1-Cyclopentene-1,2-dicarbonyl)hydrazide (54)**

¹H NMR (DMSO-d₆). 0.89 (2t, 6H, $J = 7.8$ Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 2.40 (m, 2H, -CH₂-), 2.67 (4H, m, 2x-CH₂-), 3.81 and 3.98 (2t, 4H, $J = 6.8$ Hz, 2x-NCH₂-), 4.85 (s, 2H, -OCH₂-), 7.15 (d, 2H, $J = 8.8$ Hz, Ar), 8.1 (d, 2H, $J = 8.8$ Hz, Ar); MS-FAB ($M + H^+$) 521.

**Example 44. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N-[2-[(1-Carboxy)-1-cyclohexene)-carbonyl]hydrazide (55)**

¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 (m, 6H, 3x-CH₂-), 1.74 (m, 2H, -CH₂-), 2.27 (m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.68 (s, 2H, -OCH₂-), 7.09 (d, 2H, *J* = 8.8 Hz, Ar), 8.06 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 553.

**Example 45. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N,N-(3,4,5,6-Tetrahydrophthaloyl)hydrazide (56)**

¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 (m, 2H, -CH₂-), 1.72 (m, 6H, 3x-CH₂-), 2.30 (m, 4H, 2x-CH₂-), 3.83 and 3.90 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.86 (s, 2H, -OCH₂-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.12 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 535.

**Example 46. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N,N-Phthaloylhydrazide (57)**

¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.75 (s, 2H, -OCH₂-), 7.14 (d, 2H, *J* = 8.8 Hz, Ar), 7.57 (m, 4H, Ar), 8.09 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 531

**Example 47. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N,N-Glutarylhydrazide (58)**

¹H NMR (CDCl₃). 1.05 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.75 and 1.90 (2m, 4H, 2x-CH₂-), 2.10-2.30 (m, 2H, -CH₂-), 2.80-3.10 (m, 4H, 2x-CH₂-), 4.05 and 4.16 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.80 (s, 2H, -OCH₂-), 6.75 (d, 2H, *J* = 8.8 Hz, Ar), 7.70 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 497.

**Example 48. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N,N-(3-Hydroxy)glutarylhydrazide (59)**

¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.73 (2m, 4H, 2x-CH₂-), 2.70-3.10 (m, 4H, 2x-CH₂-), 3.87 and 4.03 (2t, 4H, *J* = 6.8

Hz, -NCH₂-), 4.21 (bs, 1H, -CHOH-), 4.77 (s, 2H, -OCH₂-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.1 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 513.

Example 49. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine

5 *N*-[(4-Carboxy-(2*S*)-Trifluoroacetamido)-*n*-butanoyl]hydrazide (60)

A mixture of compound 4f (10 mg, 0.025 mmol), 7.6 mg of L-N-Boc-glutamic acid 5-*tert*-butyl ester (0.025 mmole), 7 mg of HOBt (0.05 mmole), 19 mg of DIPEA (0.15 mmole) and 15 mg of EDAC (0.078 mmole) in 1 mL of dry DMF was stirred for 8 hours at 25°C. The DMF was removed by nitrogen
10 stream. The residue was washed with 1 mL of 1 M NaHCO₃ solution and dried overnight. The crude product was suspended in 0.5 mL of CHCl₃ and 0.5 mL of TFA added. After stirring for 30 minutes at 25°C, the mixture was concentrated to dryness and dried under high vacuum. The residue was dissolved in 0.5 mL of TFAA and the solution was stirred for 30 minutes at
15 25°C. The reaction mixture was concentrated to dryness, and the residue was purified by preparative TLC (CHCl₃:MeOH=10:1) to afford 6 mg of compound 60 as a white solid (yield 40%). ¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.73 (2m, 4H, -CH₂-), 1.90-2.30 (m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.12 (m, 1H, -CH-), 4.68 (s, 2H, -OCH₂-), 7.08 (d, 2H, *J* = 8.8 Hz, Ar), 8.06 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 626.
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**Example 50. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N,N-((2*S*)-Trifluoroacetamido)glutaryl]hydrazide (61)**

25 A mixture of compound 60 (10 mg, 0.016 mmol), 7 mg of HOBt (0.05 mmole), 19 mg of DIPEA (0.15 mmole) and 15 mg of EDAC (0.078 mmole) in 1 mL of dry DMF was stirred overnight at 25°C. The reaction mixture was concentrated to dryness, and the residue was purified by preparative TLC (CHCl₃:MeOH=10:1) to afford 5 mg of compound 61 as a white solid (yield
30 53%). ¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.59 and 1.73 (2m, 4H, 2x-CH₂-), 1.90-2.30 (m, 4H, 2x-CH₂-), 3.87 and 4.02 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.81 (s, 2H, -OCH₂-), 4.18 (m, 1H, -CH-), 7.15 (d, 2H, *J* = 8.8 Hz, Ar), 8.1 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 608.

**Example 51. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N-(*N*-*tert*-Butoxycarbonyl-L-leucinyI)hydrazide (62)**

¹H NMR (DMSO-*d*₆). 0.89 (m, 13H, 2x-CH₃ and (CH₃)₂CH-), 1.35 (s, 9H, Boc), 1.42 (m, 2H, -CH₂-), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 3.85 and 4.0
 5 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.12 (m, 1H, -CH-), 4.64 (s, 2H, -OCH₂-), 7.06
 (d, 2H, *J* = 8.8 Hz, Ar), 8.05 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 614.

**Example 52. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N-(*N*-*tert*-Butoxycarbonyl-L-methionyl)hydrazide (63)**

10 ¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.25 (m, 2H, -CH₂-), 1.37 (s, 9H, Boc), 1.58 and 1.74 (2m, 4H, 2x-CH₂-), 1.88 (m, 2H, -CH₂-), 2.03 (s, 3H, -SCH₃), 3.81 and 3.98 (2t, 4H, *J* = 6.8 Hz, 2x-NCH₂-), 4.15
 (m, 1H, -CH-), 4.68 (s, 2H, -OCH₂-), 7.03 (d, 2H, *J* = 8.8 Hz, Ar), 8.03 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 632.

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**Example 53. 8-[4-[(Carboxymethyl)oxy]phenyl]-1,3-di-(*n*-propyl)xanthine
N-(*N*-Benzyloxycarbonyl-glycylglycinyI)hydrazide (64)**

¹H NMR (DMSO-*d*₆). 0.89 (2t, 6H, *J* = 7.8 Hz, 2x-CH₃), 1.58 and 1.74
 (2m, 4H, 2x-CH₂-), 3.67 (m, 1H, -CH₂- in glycine), 3.81 (m, 3H, -NCH₂- and -
 20 CH₂- in glycine), 3.98 (t, 2H, *J* = 6.8 Hz, -NCH₂-), 4.64 (s, 2H, -OCH₂-),
 5.03(s, 2H, -OCH₂-Ph), 7.03 (d, 2H, *J* = 8.8 Hz, Ar), 7.3-7.5 (m, 5H, -Ph), 8.03
 (d, 2H, *J* = 8.8 Hz, Ar); MS-FAB (*M* + *H*⁺) 649.

**Example 54. 8-[4-[(Carboxymethyl)oxy]phenyl]-1*H*-3-(*n*-propyl)xanthine
 25 Methyl Ester (65)**

To a suspension of 3.2 g of 2,5-dioxo-4-amino-3-propyl tetrahydro
 pyrimidine, 66 [prepared according to the method described in Papesch *et al.*,
J. Org. Chem., 16, 1879-1890 (1951)] (18.9 mmole), 1.5 mL of glacial acetic
 acid and 3.4 mL of 6 N HCl in 50 mL of water was added dropwise a solution
 30 of 1.38 g of sodium nitrite (20 mmole) in 5 mL of water at 0°C. The mixture
 was stirred for 1 hour and the pink precipitate was collected by filtration to
 afford 3.17 g of nitro-amine, 67 (yield 78%). ¹H NMR (DMSO-*d*₆) 0.87 (t, 3H,

$J = 7.8$ Hz, $-\text{CH}_3$), 1.51 (m, 2H, $-\text{CH}_2-$), 3.72 (t, 2H, $J = 6.8$ Hz, $-\text{NCH}_2-$), 9.12 (s, 1H, $-\text{NH}_2$).

0.086 g of nitro-amine, 67 (0.4 mmole) was hydrogenated with 10% Pd/C in 5 mL of MeOH under H_2 atmosphere (1 atm) at 25°C until the pink color disappeared (30 min). After the removal of the balloon of H_2 , 5 mL of DMF was added and the mixture was stirred for 10 min and filtered through a Celite bed.

To the solution of crude diamine, 68 was added 0.078 g of methyl 4-formylphenoxyacetate (0.4 mmole) and 0.5 mL of acetic acid. The mixture was heated at 50°C for 30 min, evaporated under reduced pressure and suspended in 20 mL of ether. The yellow precipitate (mixture of 69 and 65) was collected by filtration, dissolved in 5 mL of DMF and treated with 1 mL of aqueous solution of 0.085 g of sodium periodate (0.4 mmole) for 2 hours. After evaporation, the product was purified by crystallization in MeOH/ H_2O to afford 0.048 g of xanthine, 65 (yield 34%). ^1H NMR ($\text{DMSO}-d_6$). 0.90 (t, 3H, $J = 7.8$ Hz, $-\text{CH}_3$), 1.72 (m, 2H, $-\text{CH}_2-$), 3.71 (s, 3H, $-\text{OCH}_3$), 3.95 (t, 2H, $J = 6.8$ Hz, $-\text{NCH}_2-$), 4.89 (s, 2H, $-\text{OCH}_2-$), 7.08 (d, 2H, $J = 8.8$ Hz, Ar), 8.05 (d, 2H, $J = 8.8$ Hz, Ar), 11.07 (s, 1H, $-\text{NH}$); MS-EI (M^+) 358, Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_5$, 358.1277; Found 358.1269.

Example 55. 8-[4-[(Carboxymethyl)oxy]phenyl]-1*H*-3-(*n*-propyl)xanthine Hydrazide (70)

A solution of 0.05 g of xanthine 65 (0.14 mmole) and 0.5 mL of hydrazine anhydrous in 2 mL of dry DMF was heated overnight at 50°C . After evaporation, the residue was suspended in MeOH and the white precipitate was collected by filtration to give 0.025 g of 70 (yield 50%). m.p. = 267°C ; ^1H NMR ($\text{DMSO}-d_6$). 0.90 (t, 3H, $J = 7.8$ Hz, $-\text{CH}_3$), 1.72 (m, 2H, $-\text{CH}_2-$), 3.71 (s, 3H, $-\text{OCH}_3$), 3.95 (t, 2H, $J = 6.8$ Hz, $-\text{NCH}_2-$), 4.34 (bs, 2H, NH_2), 4.56 (s, 2H, $-\text{OCH}_2-$), 7.08 (d, 2H, $J = 8.8$ Hz, Ar), 8.05 (d, 2H, $J = 8.8$ Hz, Ar), 9.39 (s, 1H, $-\text{NH}$); MS-EI (M^+) 358, Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_6\text{O}_4$, 358.1389; Found 358.1389.

Table 5 contains data for yields and characterization of the xanthine compounds of the invention. Table 6 contains data for elemental analysis of the xanthine compounds of the invention.

Table 5. The yields and chemical characterization of xanthine derivatives.

Compound	%yield	m.p.(°C)	MS	Formula	Analysis
7	13	>310	EI:482	C ₂₇ H ₂₂ N ₄ O ₅	HRMS ^a
10	40	>310	FAB:479	C ₂₈ H ₂₂ N ₄ O ₄	C,H,N
12	71	301-302	CI:462	C ₂₅ H ₂₇ N ₃ O ₄	C,H,N
13	41	268	CI:476	C ₂₆ H ₂₉ N ₃ O ₄	C,H,N
14	46	269-270	EI:551	C ₃₂ H ₃₃ N ₃ O ₄	C,H,N
15	55	230	EI:565	C ₃₃ H ₃₅ N ₃ O ₄	C,H,N
16	49	215	FAB:476	C ₂₆ H ₂₉ N ₃ O ₄	C,H,N
17	13	225	CI:558	C ₂₇ H ₃₅ N ₃ O ₈	C,H,N
18	68	294	EI:503	C ₂₇ H ₂₉ N ₃ O ₅	C,H,N
19	29	269-270	EI:503	C ₂₇ H ₂₉ N ₃ O ₅	HRMS ^a
20	29	309-310	EI:503	C ₂₇ H ₂₉ N ₃ O ₅ •0.23H ₂ O	C,H,N
21	56	>310	CI:520	C ₂₇ H ₂₉ N ₃ O ₆	C,H,N
22	19	>310	CI:505	C ₂₆ H ₂₈ N ₆ O ₅	C,H,N
23	45	>310	FAB:519	C ₂₇ H ₃₀ N ₆ O ₅ •1.8CH ₂ Cl ₂	C,H,N
24	51	>310	FAB:506	C ₂₆ H ₂₇ N ₃ O ₆ •0.60CH ₂ Cl ₂	C,H,N
27	44	>310	CI:487	C ₂₆ H ₂₆ N ₆ O ₄	C,H,N
28	31	307	CI:507	C ₂₅ H ₂₆ N ₆ O ₆ •0.43CH ₃ OH	C,H,N
29	44	>310	CI:530	C ₂₆ H ₂₆ F ₃ N ₃ O ₄ •0.26CH ₃ OH	C,H,N
30	48	298	CI:480	C ₂₅ H ₂₆ FN ₃ O ₄	C,H,N
31	31	309	CI:496	C ₂₅ H ₂₆ ClN ₃ O ₄ •0.26(CH ₃) ₂ CO	C,H,N
32	36	>310	CI:540	C ₂₅ H ₂₆ BrN ₃ O ₄	C,H,N
33	13	>310	CI:588	C ₂₅ H ₂₆ IN ₃ O ₄ •0.60CH ₃ OH	C,H,N
4c	79	>310	FAB:509	C ₂₅ H ₂₈ N ₆ O ₆	C,H,N
34	49	302-303	EI:504	C ₂₆ H ₂₈ N ₆ O ₅	C,H,N
35	42	281-283	CI:500	C ₂₈ H ₂₉ N ₃ O ₄ •0.27MeOH	C,H,N
36	33	305	FAB:608	C ₃₆ H ₄₁ N ₃ O ₄	HRMS ^a
37	76	308-309	CI:596	C ₃₆ H ₂₉ N ₃ O ₄ •0.60H ₂ O	C,H,N
38	18	284	EI:599	C ₃₅ H ₂₉ N ₃ O ₅	HRMS ^a

a) High-resolution mass in EI or FAB⁺ mode (*m/z*) determined to be within acceptable limits: 7: calcd, 482.1590; found, 482.1597, 19: calcd, 503.2169; found, 503.2169, 36: calcd, 608.3237; found, 608.3251; 38: calcd, 599.2169; found, 599.2171.

Table 6. Elemental Analysis of Xanthine Derivatives

Compound No.	Formula	MW (anhyd)	Calculated (% or HRMS)	Found (% or HRMS)
7	$C_{27}H_{22}N_4O_3$	482.49	482.1590	482.1597
10	$C_{28}H_{22}N_4O_4$	478.50	C70.28, H4.63, N11.70	C70.16, H4.72, N11.72
12	$C_{25}H_{27}N_3O_4$	461.52	C65.06, H5.90, N15.17	C65.04, H5.93, N15.20
13	$C_{26}H_{29}N_3O_4$	475.54	C65.66, H6.15, N14.72	C65.70, H6.22, N14.72
14	$C_{32}H_{33}N_3O_4$	551.64	C69.67, H6.03, N12.69	C69.60, H6.08, N12.66
15	$C_{33}H_{35}N_3O_4$	565.67	C70.06, H6.24, N12.38	C70.01, H6.33, N12.35
16	$C_{26}H_{29}N_3O_4$	475.54	C65.66, H6.15, N14.72	C65.45, H6.23, N14.68
17	$C_{27}H_{31}N_3O_4$	557.60	C58.15, H6.33, N12.56	C57.93, H6.38, N12.41
18	$C_{27}H_{29}N_3O_5$	503.55	C64.40, H5.81, N13.90	C64.24, H5.83, N13.87
19	$C_{27}H_{29}N_3O_5$	503.55	503.2169	503.2169
20	$C_{27}H_{29}N_3O_5$	503.55	C64.40, H5.81, N13.90	
	$C_{27}H_{29}N_3O_5 \cdot 0.23H_2O$	507.70	C63.88, H5.85, N13.79	C63.74, H5.77, N13.80
21	$C_{27}H_{29}N_3O_6$	519.55	C62.41, H5.63, N13.48	C62.58, H5.67, N13.36
22	$C_{26}H_{28}N_4O_5$	504.54	C61.89, H5.59, N16.65	C60.64, H5.66, N15.58
23	$C_{27}H_{30}N_6O_5$	518.57	C62.53, H5.83, N16.20	
	$C_{27}H_{30}N_6O_5 \cdot 1.80CH_2Cl_2$	671.45	C51.51, H5.04, N12.51	C51.75, H4.92, N12.77
24	$C_{26}H_{27}N_3O_6$	505.53	C61.77, H5.38, N13.85	
	$C_{26}H_{27}N_3O_6 \cdot 0.60CH_2Cl_2$	556.49	C57.41, H5.11, N12.58	C57.12, H5.18, N12.46
27	$C_{26}H_{26}N_6O_4$	486.53	C64.18, H5.39, N17.27	C64.27, H5.47, N17.03
28	$C_{23}H_{26}N_6O_6$	506.51	C59.28, H5.17, N16.59	
	$C_{23}H_{26}N_6O_6 \cdot 0.43CH_3OH$	520.30	C58.70, H5.37, N16.15	C58.63, H5.26, N15.98
29	$C_{26}H_{26}F_3N_3O_4$	529.51	C58.97, H4.95, N13.22	
	$C_{26}H_{26}F_3N_3O_4 \cdot 0.26CH_3OH$	537.85	C58.64, H5.07, N13.02	C58.74, H5.07, N12.96
30	$C_{23}H_{26}FN_3O_4$	479.51	C62.62, H5.47, N14.60	C62.39, H5.49, N14.31
31	$C_{23}H_{26}ClN_3O_4$	495.96	C60.54, H5.28, N14.12	
	$C_{23}H_{26}ClN_3O_4 \cdot 0.26(CH_3)_2CO$	511.07	C60.59, H5.44, N13.70	C60.59, H5.40, N13.62
32	$C_{23}H_{26}BrN_3O_4$	540.41	C55.56, H4.85, N12.95	C55.28, H4.89, N12.70
33	$C_{23}H_{26}IN_3O_4$	587.41	C51.11, H4.46, N11.92	
	$C_{23}H_{26}IN_3O_4 \cdot 0.60CH_3OH$	606.64	C50.68, H4.72, N11.54	C50.48, H4.40, N11.28
4c	$C_{23}H_{28}N_6O_6$	508.53	C59.04, H5.55, N16.52	C58.79, H5.50, N16.48
34	$C_{26}H_{28}N_6O_5$	504.54	C61.89, H5.59, N16.65	C62.18, H5.86, N16.31
35	$C_{27}H_{29}N_3O_4$	499.56	C67.31, H5.85, N14.01	
	$C_{27}H_{29}N_3O_4 \cdot 0.27MeOH$	508.22	C66.81, H5.97, N13.78	C66.73, H5.87, N13.61
36	$C_{36}H_{41}N_3O_4$	607.75	608.3237 (M+H)	608.3251
37	$C_{36}H_{39}N_3O_4$	595.65	C72.59, H4.91, N11.75	
	$C_{36}H_{39}N_3O_4 \cdot 0.60H_2O$	606.47	C71.30, H5.02, N11.55	C71.48, H4.98, N11.45
38	$C_{35}H_{39}N_3O_5$	599.64	599.2169	599.2171

Example 56 Prevention of Myocardial Necrosis Following Ninety Minute LAD Occlusion by 8-[4-(((4-Cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (27).

The compounds of the invention were tested for their ability to block A_{2B} receptors to show that mast cell degranulation can be reduced or prevented. In addition, this example shows that these antagonists could prevent or markedly attenuate the extent of myocardial infarction that occurred during coronary artery occlusion.

The left anterior descending (LAD) coronary artery of a group of dogs was isolated and encircled with a snare occluder. The dogs LAD artery blood supply was occluded for 90 minutes. The test solutions were administered intracoronary beginning immediately prior to the 90 minute occlusion interval and continued for two hours post-reperfusion (Figure 6). One group of three dogs were administered a solution containing the (4-cyano)phenyl compound, prepared in Example 18, infused at a concentration of 200nM at a rate of 1.0 mL /min. by intracoronary (i.c.) infusion into the LAD. A second group of four dogs were administered a solution containing the vehicle (carrier). Regional myocardial blood flow was measured at baseline, during LAD occlusion and for 2 hrs after reperfusion using radiolabeled microspheres (mic).

The results are illustrated in Figures 7 and 8. These figures show that the infusion of the test compound during the 90 minute occlusion dramatically attenuated infarct size compared with dogs that were untreated.

Example 57 Specific binding of tritiated 8-[4-(((4-cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (27).

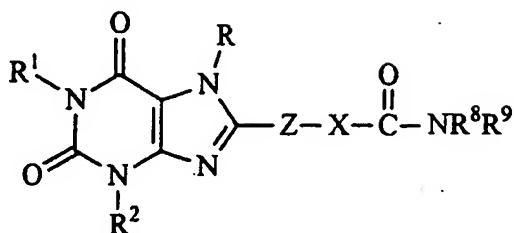
The compounds of the invention were tested for their specific binding at A_{2B} receptors. Compound 27, 8-[4-(((4-cyano)phenylcarbamoylmethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine was tritiated by New England Nuclear. The tritiated compound was used in radioligand binding assays on rat bladder membranes as described hereinabove substituting rat bladder cells for the cultured cells. The results show that specific binding (483 fmol/mg protein) with a K_D of 1.82 nM of the test compound in the tissue was detected.

The results are illustrated in Figure 9. This is a plot of the bound test compound vs. the unbound test compound. The graph shows both specific and nonspecific binding.

- 5 All patents, patent applications, books and literature cited in the specification are hereby incorporated by reference in their entirety. In the case of any inconsistencies, the present disclosure, including any definitions therein will prevail. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be
- 10 understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

WHAT IS CLAIMED IS:

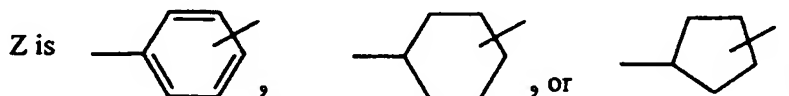
1. A compound of formula I:



I

5

wherein R, and R¹ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, heterocycle, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or heteroaryl;



- 10 X is (C₁-C₈)alkylene, (C₂-C₈)alkenylene, (C₂-C₈)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R⁴)C(O)—, —OC(O)—, —N(R⁵)(R⁶)—, —S—, —S(O)— or —SO₂—,

- 15 R² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heterocycle or heteroaryl; wherein R² is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH₂, —NHR⁷, —CN, —COOH and —SO₃H,

- 20 wherein R⁴, R⁵, R⁶ and R⁷ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or halo(C₁-C₆)alkyl; and

wherein R^8 is hydrogen, (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, (C_7-C_{18}) aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$;
or

R^8 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

R^8 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; and

wherein R^9 is $-NR^{10}R^{11}$, or R^9 is (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, (C_7-C_{18}) aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; or

R^9 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

R^9 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$,

$-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$,
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$, and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8) alkyl,
 (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heterocycle,
 5 heteroaryl, $-\text{C}(\text{O})(\text{CH}_2)_n\text{CO}_2\text{R}^{12}$, $-\text{C}(\text{O})\text{CR}^{21}=\text{CR}^{22}(\text{CH}_2)_m\text{CO}_2\text{R}^{12}$,
 $-\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})(\text{C}_3-\text{C}_8)$ cycloalkyl or $-\text{C}(\text{O})(\text{C}_3-\text{C}_8)$ cycloalkenyl, each
 optionally substituted with one or more substituents, wherein the substituents
 independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl,
 $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$,
 10 $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$,
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; or the R^{10} and R^{11} groups and
 the nitrogen atom can be taken together to form a heterocyclic ring or a
 heteroaryl ring, each ring optionally substituted with one or more substituents,
 wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_8) alkyl,
 15 (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$,
 $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$,
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; wherein n is 1 to 6, and m is 0
 to 4;

R^{12} is hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl,
 20 (C_3-C_8) cycloalkyl, $(\text{C}_4-\text{C}_{16})$ cycloalkylalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl,
 heterocycle, or heteroaryl,

wherein the R^{12} group is optionally substituted with one or more
 substituents independently selected from the group consisting of oxo,
 (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl,
 25 heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$,
 $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$;

wherein R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{23} and R^{24} are
 independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl,
 $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl or halo (C_1-C_8) alkyl;

30 wherein R^{21} and R^{22} are independently hydrogen, (C_1-C_8) alkyl,
 (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl;

provided that $-\text{NR}^8\text{R}^9$ is not aminoalkyl, aminodialkyl or hydrazino;

and

provided that when R and R⁸ are both H, and R¹ and R² are both alkyl, R⁹ is not 2-hydroxyethyl, 2-thioethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or a pharmaceutically acceptable salt thereof.

5

2. The compound according to claim 1, wherein R and R¹ are independently hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyl, (C₆-C₁₀)cycloalkylalkyl, heterocycle, (C₆)aryl, (C₇-C₁₀)aralkyl or heteroaryl;

10 X is (C₁-C₆)alkylene, (C₂-C₆)alkenylene, (C₂-C₆)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R⁴)C(O)—, —OC(O)—, —N(R⁵)(R⁶)—, —S—, —S(O)— or —SO₂—;

R² is hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, (C₆-C₁₀)cycloalkylalkyl, (C₆)aryl, (C₇-C₁₀)aralkyl or a heterocycle;

15

wherein R⁴, R⁵, R⁶ and R⁷ are independently hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₃-C₆)cycloalkyl, (C₆)aryl, (C₇-C₁₀)aralkyl or halo(C₁-C₆)alkyl groups; and

20 wherein R⁸ is hydrogen, (C₃-C₆)cycloalkyl, (C₃-C₁₀)cycloalkylalkyl, (C₇-C₁₀)aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆)aryl, (C₇-C₁₀)aralkyl, heteroaryl, halo, —OR¹⁵, —CN, —NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶,
 25 —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H;
 or

R⁸ is (C₁-C₆)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C₂-C₆)alkenyl, (C₆)aryl, (C₇-C₁₀)aralkyl, heteroaryl, halo, —OR¹⁵, —CN, —NO₂,
 30 —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ and —SO₃H; or

R⁸ is (C₆-C₁₀)aryl, substituted with one or more substituents independently selected from the group consisting of (C₁-C₆)alkyl, halo(C₁-

C_6)alkyl, (C_2-C_6) alkenyl, (C_7-C_{10}) aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

- R^9 is $-NR^{10}R^{11}$, or R^9 is (C_3-C_6) cycloalkyl, (C_4-C_{10}) cycloalkylalkyl,
 5 (C_7-C_{10}) aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_6) aryl, (C_7-C_{10}) aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$;

10 or

- R^9 is (C_1-C_6) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_6) alkenyl, (C_6) aryl, (C_7-C_{10}) aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$,
 15 $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

- R^9 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_7-C_{10}) aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$,
 20 $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

- wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_4) alkyl, (C_2-C_4) alkenyl, (C_3-C_6) cycloalkyl, (C_6) aryl, (C_7-C_{10}) aralkyl, heterocycle, heteroaryl, $-C(O)(CH_2)_nCO_2R^{12}$, $-C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$, $-C(O)R^{12}$, $-C(O)(C_3-C_6)$ cycloalkyl or $-C(O)(C_3-C_6)$ cycloalkenyl, each
 25 optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_6) aryl, (C_7-C_{10}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; or the R^{10} and R^{11} groups and
 30 the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_6) aryl, (C_7-C_{10}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$,

$-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$,
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$.

3. The compound according to claim 2, wherein R, R¹ and R² are
 5 independently hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl,
 (C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, (C₆-C₁₀)cycloalkylalkyl, (C₆)aryl, or
 (C₇-C₁₀)aralkyl;



- X is O-(C₁-C₇)alkylene, O-(C₂-C₇)alkenylene, (C₁-C₈)alkylene or
 10 (C₂-C₈)alkenylene; wherein

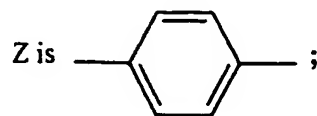
- R⁹ is (C₃-C₆)cycloalkyl, (C₄-C₁₀)cycloalkylalkyl, (C₇-C₁₀)aralkyl,
 heterocycle or heteroaryl, each optionally substituted with one or more
 substituents, wherein the substituents independently are oxo, (C₁-C₆)alkyl,
 halo(C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₆)aryl, (C₇-C₁₀)aralkyl, heteroaryl, halo,
 15 $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$,
 $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; or

- R⁹ is (C₁-C₆)alkyl, substituted with one or more substituents
 independently selected from the group consisting of oxo, (C₂-C₆)alkenyl,
 (C₆)aryl, (C₇-C₁₀)aralkyl, heteroaryl, halo, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$,
 20 $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$,
 $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; or

- R⁹ is (C₆-C₁₀)aryl, substituted with one or more substituents
 independently selected from the group consisting of (C₁-C₆)alkyl, halo(C₁-
 C₆)alkyl, (C₂-C₆)alkenyl, (C₇-C₁₀)aralkyl, heteroaryl, halo, $-\text{OR}^{15}$, $-\text{CN}$,
 25 $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$,
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$.

4. The compound according to claim 2, wherein R, R¹ and R² are
 independently hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl,

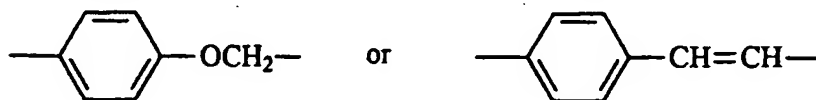
(C₁-C₄)alkoxy, (C₅-C₆)cycloalkyl, (C₆-C₁₀)cycloalkylalkyl, (C₆)aryl, or (C₇-C₁₀)aralkyl;



X is O-(C₁-C₇)alkylene, O-(C₂-C₇)alkenylene, (C₁-C₈)alkylene or (C₂-C₈)alkenylene; and

R⁹ is —NR¹⁰R¹¹.

5. The compound according to claim 3, wherein —X—Z— is



R¹ and R² are independently —CH₂CH₃, —CH₂CH=CH₂,
10 —CH₂CH₂CH₃ or cyclohexylmethyl.

6. The compound according to claim 5, wherein aryl is phenyl and aralkyl is benzyl.

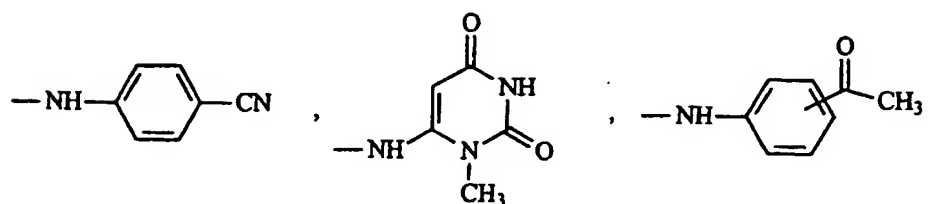
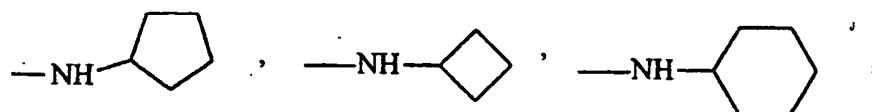
15 7. The compound according to claim 6, wherein R⁹ is phenyl substituted with 1-3 substituents that are independently trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, benzyl, F, Cl, Br, I, —CN, —NO₂, —CO₂R¹⁵, —C(O)R¹⁶, —NR¹³R¹⁴ or —C(O)NR¹⁷R¹⁸, or benzyl, optionally substituted with 1-3 substituents that are
20 independently alkyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, —OH, F, Cl, Br, I, —CN, —NO₂, —CO₂R¹⁵, —C(O)R¹⁶, —NR¹³R¹⁴ or —C(O)NR¹⁷R¹⁸.

8. The compound according to claim 7, wherein R⁸ is hydrogen and R⁹ is
25 phenyl substituted with 1-3 substituents that are independently F, Cl, Br, I,

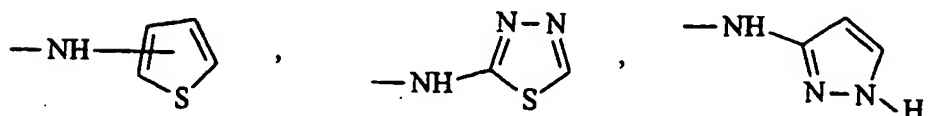
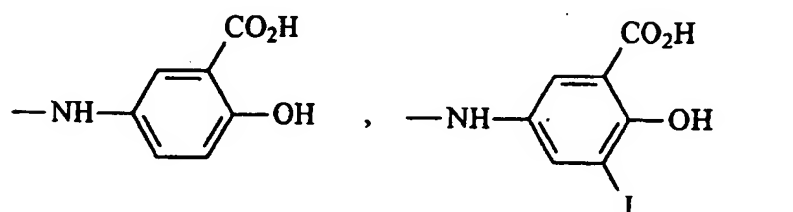
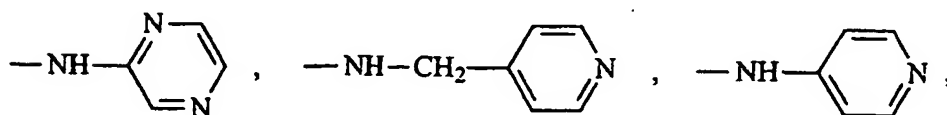
—CN, —COOH, —C(O)OCH₃, —C(O)CH₂CH₃, —C(O)CH₃, —C(O)NH₂ or
—C(O)NHCH₃ or

benzyl, optionally substituted with 1-3 substituents that are
independently —CH₂CH₃, F, Cl, Br, I, —CN, —COOH, —CO₂CH₃,
5 —C(O)CH₂CH₃, —C(O)CH₃, —C(O)NH₂ or —C(O)NHCH₃.

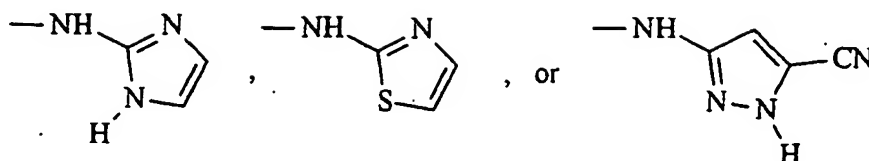
9. The compound according to claim 5, wherein —NR⁸R⁹ is



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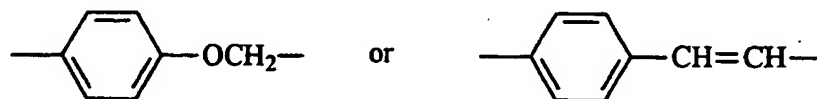
73



10. The compound according to claim 9, wherein R is H, R¹ and R² are each —CH₂CH=CH₂, and R⁹ is 4-cyanophenyl.

11. The compound according to claim 9, wherein R is H, R¹ and R² are each —CH₂CH₂CH₃, and R⁹ is 3-carboxy-4-hydroxyphenyl or 3-acetylphenyl.

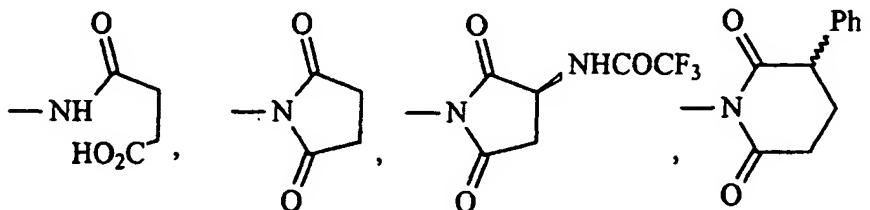
12. The compound according to claim 4, wherein —X—Z— is



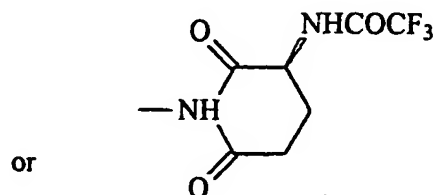
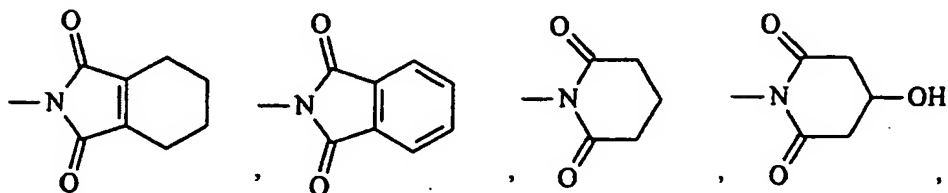
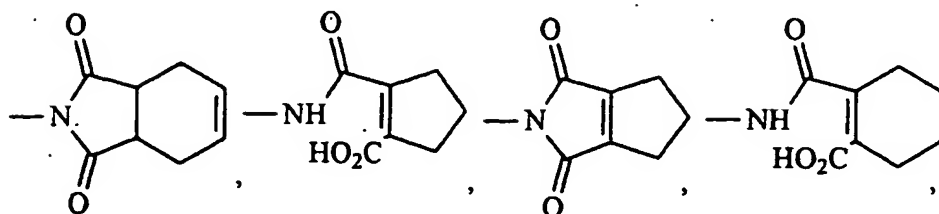
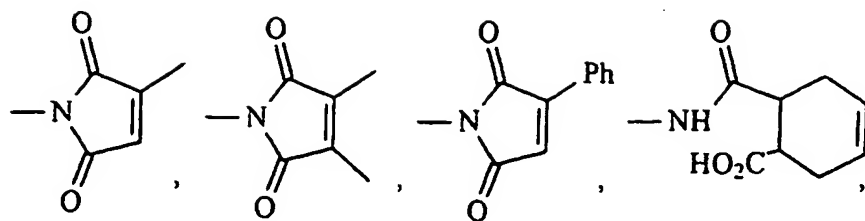
10 R¹ and R² are independently —CH₂CH₃, —CH₂CH=CH₂, —CH₂CH₂CH₃, or cyclohexylmethyl; and R⁸ is hydrogen, aryl or aralkyl.

13. The compound according to claim 12, wherein R¹⁰ and R¹¹ are independently hydrogen, —C(O)(CH₂)_nCO₂R¹², —C(O)CR²¹=CR²²CO₂R¹², —C(O)R¹², —C(O)(C₃-C₆)cycloalkyl, —C(O)(C₃-C₆)cycloalkenyl or wherein the R¹⁰ and R¹¹ groups and the nitrogen atom taken together form said optionally substituted heterocycle or a heteroaryl ring, and n is 2.

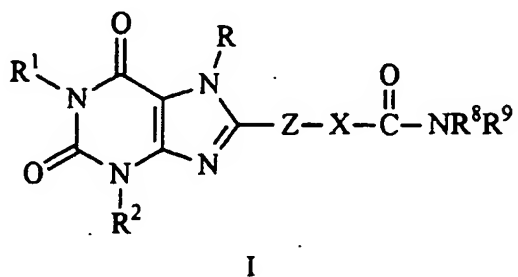
20 14. The compound of claim 13, wherein R⁹ is



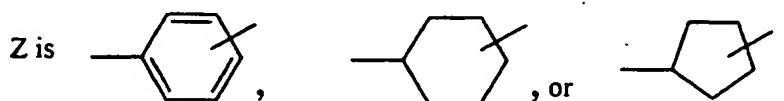
74



5 15. A compound of formula I:



wherein R and R¹ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, heterocycle, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or heteroaryl;



5 X is (C₁-C₈)alkylene, (C₂-C₈)alkenylene, (C₂-C₈)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R⁴)C(O)—, —OC(O)—, —N(R⁵)(R⁶)—, —S—, —S(O)— or —SO₂—,

R² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heterocycle or heteroaryl; wherein R² is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH₂, —NHR⁷, —CN, —COOH and —SO₃H,

15 wherein R⁴, R⁵, R⁶ and R⁷ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or halo(C₁-C₆)alkyl; and

wherein R⁸ is hydrogen, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₇-C₁₈)aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, halo, —OR¹⁵, —CN, —NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H; or

25 R⁸ is (C₁-C₈)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ and —SO₃H; or

R^8 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$,
 5 $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; and

wherein R^9 is (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, (C_7-C_{18}) aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$,
 10 $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; or

R^9 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$,
 15 $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

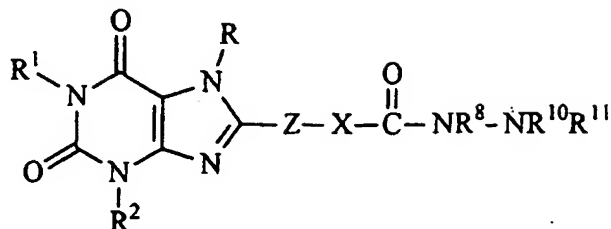
R^9 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$,
 20 $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; and

wherein, R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{23} and R^{24} are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl or halo (C_1-C_8) alkyl;
 25

provided that $-NR^8R^9$ is not aminoalkyl or aminodialkyl; and

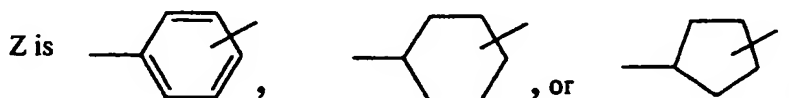
provided that when R and R^8 are both H, and R^1 and R^2 are both alkyl, R^9 is not 2-hydroxyethyl, 2-thiolethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or
 30 a pharmaceutically acceptable salt thereof.

16. A compound of formula II:



II

wherein R and R¹ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, heterocycle, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or heteroaryl;



X is (C₁-C₈)alkylene, (C₂-C₈)alkenylene, (C₂-C₈)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R⁴)C(O)—, —OC(O)—, —N(R⁵)(R⁶)—, —S—, —S(O)— or —SO₂—,

R² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heterocycle or heteroaryl; wherein R² is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH₂, —NHR⁷, —CN, —COOH and —SO₃H,

wherein R⁴, R⁵, R⁶ and R⁷ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or halo(C₁-C₆)alkyl; and

wherein R⁸ is hydrogen, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₇-C₁₈)aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C₁-C₈)alkyl, (C₁-C₈)alkoxy, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-

C_{18})aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; or

R^8 is (C_1-C_8) alkyl, substituted with one or more substituents

- 5 independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

R^8 is (C_6-C_{10}) aryl, substituted with one or more substituents

- 10 independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; and

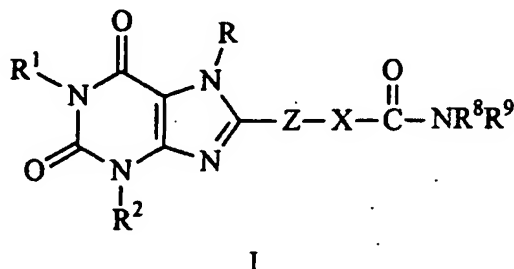
wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8) alkyl,

- 15 (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-C(O)(CH_2)_nCO_2R^{12}$, $-C(O)CR^{21}=CR^{22}(CH_2)_mCO_2R^{12}$, $-C(O)R^{12}$, $-C(O)(C_3-C_8)$ cycloalkyl or $-C(O)(C_3-C_8)$ cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl,
- 20 (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; or the R^{10} and R^{11} groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents,
- 25 wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; wherein n is 1 to 6, and m is 0 to 4;

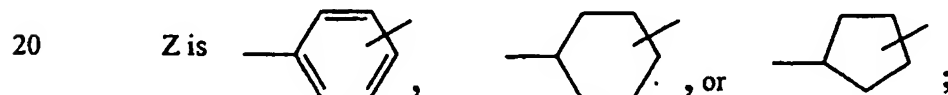
- 30 R^{12} is hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heterocycle, or heteroaryl,

- wherein the R^{12} group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$,
 5 $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$;
 wherein R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{23} and R^{24} are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl or halo (C_1-C_6) alkyl;
 R^{21} and R^{22} are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl,
 10 (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl;
 provided that $-NR^8-NR^{10}R^{11}$ is not hydrazino; or
 a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound of formula I:
 15



wherein R , and R^1 are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_8) alkoxy, (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, heterocycle, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl or heteroaryl;



X is (C_1-C_8) alkylene, (C_2-C_8) alkenylene, (C_2-C_8) alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is

optionally replaced with a group having the formula —O— , $\text{—N(R}^4\text{)C(O)—}$, —OC(O)— , $\text{—N(R}^5\text{)(R}^6\text{)—}$, —S— , —S(O)— or $\text{—SO}_2\text{—}$,

R^2 is hydrogen, $(\text{C}_1\text{—C}_8)\text{alkyl}$, $(\text{C}_2\text{—C}_8)\text{alkenyl}$, $(\text{C}_2\text{—C}_8)\text{alkynyl}$, $(\text{C}_1\text{—C}_8)\text{-alkoxy}$, $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$, $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$, $(\text{C}_6\text{—C}_{10})\text{aryl}$,

- 5 $(\text{C}_7\text{—C}_{18})\text{aralkyl}$, heterocycle or heteroaryl; wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of —OH , —SH , —NH_2 , —NHR^7 , —CN , —COOH and $\text{—SO}_3\text{H}$,

wherein R^4 , R^5 , R^6 and R^7 are independently hydrogen, $(\text{C}_1\text{—C}_8)\text{alkyl}$, $(\text{C}_2\text{—C}_8)\text{alkenyl}$, $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$, $(\text{C}_6\text{—C}_{10})\text{aryl}$, $(\text{C}_7\text{—C}_{18})\text{aralkyl}$ or

- 10 $\text{halo}(\text{C}_1\text{—C}_6)\text{alkyl}$; and

wherein R^8 is hydrogen, $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$, $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$, $(\text{C}_7\text{—C}_{18})\text{aralkyl}$, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(\text{C}_1\text{—C}_8)\text{alkyl}$, $\text{halo}(\text{C}_1\text{—C}_6)\text{alkyl}$, $(\text{C}_2\text{—C}_8)\text{alkenyl}$, $(\text{C}_6\text{—C}_{10})\text{aryl}$, $(\text{C}_7\text{—C}_{18})\text{aralkyl}$,

- 15 heteroaryl, halo, —OR^{15} , —CN , —NO_2 , $\text{—CO}_2\text{R}^{15}$, —OC(O)R^{16} , —C(O)R^{16} , $\text{—NR}^{13}\text{R}^{14}$, $\text{—N(R}^{23}\text{)C(O)R}^{24}$, $\text{—C(O)NR}^{17}\text{R}^{18}$, —SR^{19} , $\text{—SO}_2\text{R}^{20}$ or $\text{—SO}_3\text{H}$;
or

R^8 is $(\text{C}_1\text{—C}_8)\text{alkyl}$, substituted with one or more substituents independently selected from the group consisting of oxo, $(\text{C}_2\text{—C}_8)\text{alkenyl}$,

- 20 $(\text{C}_6\text{—C}_{10})\text{aryl}$, $(\text{C}_7\text{—C}_{18})\text{aralkyl}$, heteroaryl, —OR^{15} , halo, —CN , —NO_2 , —OC(O)R^{16} , —C(O)R^{16} , $\text{—NR}^{13}\text{R}^{14}$, $\text{—N(R}^{23}\text{)C(O)R}^{24}$, $\text{—C(O)NR}^{17}\text{R}^{18}$, —SR^{19} , $\text{—SO}_2\text{R}^{20}$ and $\text{—SO}_3\text{H}$; or

R^8 is $(\text{C}_6\text{—C}_{10})\text{aryl}$, substituted with one or more substituents

- independently selected from the group consisting of $(\text{C}_1\text{—C}_8)\text{alkyl}$, $\text{halo}(\text{C}_1\text{—C}_6)\text{alkyl}$, $(\text{C}_2\text{—C}_8)\text{alkenyl}$, $(\text{C}_7\text{—C}_{18})\text{aralkyl}$, heteroaryl, —OR^{15} , —CN , —NO_2 , $\text{—CO}_2\text{R}^{15}$, —OC(O)R^{16} , —C(O)R^{16} , $\text{—NR}^{13}\text{R}^{14}$, $\text{—N(R}^{23}\text{)C(O)R}^{24}$, $\text{—C(O)NR}^{17}\text{R}^{18}$, —SR^{19} , $\text{—SO}_2\text{R}^{20}$ and $\text{—SO}_3\text{H}$; and

wherein R^9 is $\text{—NR}^{10}\text{R}^{11}$, or R^9 is $(\text{C}_3\text{—C}_8)\text{cycloalkyl}$, $(\text{C}_4\text{—C}_{16})\text{cycloalkylalkyl}$, $(\text{C}_7\text{—C}_{18})\text{aralkyl}$, heterocycle or heteroaryl, each optionally

- 30 substituted with one or more substituents, wherein the substituents independently are oxo, $(\text{C}_1\text{—C}_8)\text{alkyl}$, $\text{halo}(\text{C}_1\text{—C}_6)\text{alkyl}$, $(\text{C}_2\text{—C}_8)\text{alkenyl}$, $(\text{C}_6\text{—C}_{10})\text{aryl}$, $(\text{C}_7\text{—C}_{18})\text{aralkyl}$, heteroaryl, —OR^{15} , halo, —CN , —NO_2 , $\text{—CO}_2\text{R}^{15}$,

—OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸,
—SR¹⁹, —SO₂R²⁰ or —SO₃H; or

R⁹ is (C₁-C₈)alkyl, substituted with one or more substituents
independently selected from the group consisting of oxo, (C₂-C₈)alkenyl,
5 (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂,
—OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸,
—SR¹⁹, —SO₂R²⁰ and —SO₃H; or

R⁹ is (C₆-C₁₀)aryl, substituted with one or more substituents
independently selected from the group consisting of (C₁-C₈)alkyl, halo(C₁-
10 C₈)alkyl, (C₂-C₈)alkenyl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, —CN, —NO₂,
—CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴,
—C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ and —SO₃H, and

wherein R¹⁰ and R¹¹ are independently hydrogen, (C₁-C₈)alkyl,
(C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heterocycle,
15 heteroaryl, —C(O)(CH₂)_nCO₂R¹², —C(O)CR²¹=CR²²(CH₂)_mCO₂R¹²,
—C(O)R¹², —C(O)(C₃-C₈)cycloalkyl or —C(O)(C₃-C₈)cycloalkenyl, each
optionally substituted with one or more substituents, wherein the substituents
independently are oxo, (C₁-C₈)alkyl, halo(C₁-C₈)alkyl, (C₂-C₈)alkenyl,
(C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂,
20 —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴,
—C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H; or the R¹⁰ and R¹¹ groups and
the nitrogen atom can be taken together to form a heterocyclic ring or a
heteroaryl ring, each ring optionally substituted with one or more substituents,
wherein the substituents independently are oxo, (C₁-C₈)alkyl, halo(C₁-C₈)alkyl,
25 (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN,
—NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴,
—C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H; wherein n is 1 to 6, and m is 0
to 4;

R¹² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,
30 (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl,
heterocycle, or heteroaryl,

wherein the R¹² group is optionally substituted with one or more
substituents independently selected from the group consisting of oxo, (C₁-C₈)-

alkyl, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H;

wherein R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²³ and R²⁴ are

- 5 independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or halo(C₁-C₆)alkyl;

wherein R²¹ and R²² are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl;

provided that —NR⁸R⁹ is not aminoalkyl, aminodialkyl or

- 10 hydrazino; and

provided that when R and R⁸ are both H, and R¹ and R² are both alkyl, R⁹ is not 2-hydroxyethyl, 2-thioethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or

a pharmaceutically acceptable salt thereof in combination with a

- 15 pharmaceutically acceptable carrier.

18. The composition according to claim 17, wherein R and R¹ are independently hydrogen, (C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyl, (C₆-C₁₀)cycloalkylalkyl, heterocycle,

- 20 (C₆)aryl, (C₇-C₁₀)aralkyl or heteroaryl;

X is (C₁-C₆)alkylene, (C₂-C₆)alkenylene, (C₂-C₆)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R⁴)C(O)—, —OC(O)—, —N(R⁵)(R⁶)—, —S—, —S(O)— or —SO₂—;

- 25 R² is hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, (C₆-C₁₀)cycloalkylalkyl, (C₆)aryl, (C₇-C₁₀)aralkyl or a heterocycle;

wherein R⁴, R⁵, R⁶ and R⁷ are independently hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₃-C₆)cycloalkyl, (C₆)aryl, (C₇-C₁₀)aralkyl or halo(C₁-C₆)alkyl

- 30 groups; and

wherein R⁸ is hydrogen, (C₃-C₆)cycloalkyl, (C₄-C₁₀)cycloalkylalkyl, (C₇-C₁₀)aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C₁-

C_6)alkyl, halo(C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_6)aryl, (C_7 - C_{10})aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; or

5 R^8 is (C_1 - C_6)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2 - C_6)alkenyl, (C_6)aryl, (C_7 - C_{10})aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

10 R^8 is (C_6 - C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1 - C_6)alkyl, halo(C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_7 - C_{10})aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

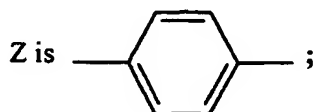
15 R^9 is $-NR^{10}R^{11}$, or R^9 is (C_3 - C_6)cycloalkyl, (C_4 - C_{10})cycloalkylalkyl, (C_7 - C_{10})aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1 - C_6)alkyl, halo(C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_6)aryl, (C_7 - C_{10})aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$,
20 $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$; or

R^9 is (C_1 - C_6)alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2 - C_6)alkenyl, (C_6)aryl, (C_7 - C_{10})aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$,
25 $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

R^9 is (C_6 - C_{10})aryl, substituted with one or more substituents independently selected from the group consisting of (C_1 - C_6)alkyl, halo(C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_7 - C_{10})aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$,
30 $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

wherein R^{10} and R^{11} are independently hydrogen, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_3 - C_6)cycloalkyl, (C_6)aryl, (C_7 - C_{10})aralkyl, heterocycle,

- heteroaryl, $-\text{C}(\text{O})(\text{CH}_2)_n\text{CO}_2\text{R}^{12}$, $-\text{C}(\text{O})\text{CR}^{21}=\text{CR}^{22}(\text{CH}_2)_m\text{CO}_2\text{R}^{12}$,
 $-\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})(\text{C}_3-\text{C}_6)\text{cycloalkyl}$ or $-\text{C}(\text{O})(\text{C}_3-\text{C}_6)\text{cycloalkenyl}$, each
optionally substituted with one or more substituents, wherein the substituents
independently are oxo, $(\text{C}_1-\text{C}_6)\text{alkyl}$, halo $(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_2-\text{C}_6)\text{alkenyl}$, $(\text{C}_6)\text{aryl}$,
5 $(\text{C}_7-\text{C}_{10})\text{aralkyl}$, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$,
 $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$,
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; or the R^{10} and R^{11} groups and
the nitrogen atom can be taken together to form a heterocyclic ring or a
heteroaryl ring, each ring optionally substituted with one or more substituents,
10 wherein the substituents independently are oxo, $(\text{C}_1-\text{C}_6)\text{alkyl}$, halo $(\text{C}_1-\text{C}_6)\text{alkyl}$,
 $(\text{C}_2-\text{C}_6)\text{alkenyl}$, $(\text{C}_6)\text{aryl}$, $(\text{C}_7-\text{C}_{10})\text{aralkyl}$, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$,
 $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$,
 $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$.
- 15 19. The composition according to claim 18, wherein R , R^1 and R^2 are
independently hydrogen, $(\text{C}_1-\text{C}_4)\text{alkyl}$, $(\text{C}_2-\text{C}_4)\text{alkenyl}$, $(\text{C}_2-\text{C}_4)\text{alkynyl}$,
 $(\text{C}_1-\text{C}_4)\text{alkoxy}$, $(\text{C}_5-\text{C}_6)\text{cycloalkyl}$, $(\text{C}_6-\text{C}_{10})\text{cycloalkylalkyl}$, $(\text{C}_6)\text{aryl}$, or
 $(\text{C}_7-\text{C}_{10})\text{aralkyl}$;



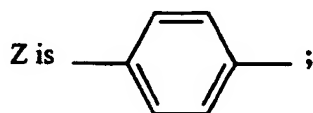
- 20 X is $\text{O}-(\text{C}_1-\text{C}_7)\text{alkylene}$, $\text{O}-(\text{C}_2-\text{C}_7)\text{alkenylene}$, $(\text{C}_1-\text{C}_6)\text{alkylene}$ or
 $(\text{C}_2-\text{C}_6)\text{alkenylene}$; wherein
 R^9 is $(\text{C}_3-\text{C}_6)\text{cycloalkyl}$, $(\text{C}_4-\text{C}_{10})\text{cycloalkylalkyl}$, $(\text{C}_7-\text{C}_{10})\text{aralkyl}$,
heterocycle or heteroaryl, each optionally substituted with one or more
substituents, wherein the substituents independently are oxo, $(\text{C}_1-\text{C}_6)\text{alkyl}$,
25 halo $(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_2-\text{C}_6)\text{alkenyl}$, $(\text{C}_6)\text{aryl}$, $(\text{C}_7-\text{C}_{10})\text{aralkyl}$, heteroaryl, halo,
 $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$,
 $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; or
 R^9 is $(\text{C}_1-\text{C}_6)\text{alkyl}$, substituted with one or more substituents
independently selected from the group consisting of oxo, $(\text{C}_2-\text{C}_6)\text{alkenyl}$,

(C₆)aryl, (C₇-C₁₀)aralkyl, heteroaryl, halo, —OR¹⁵, —CN, —NO₂,
 —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸,
 —SR¹⁹, —SO₂R²⁰ and —SO₃H; or

R⁹ is (C₆-C₁₀)aryl, substituted with one or more substituents

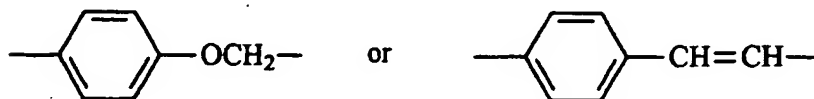
- 5 independently selected from the group consisting of (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₇-C₁₀)aralkyl, heteroaryl, halo, —OR¹⁵, —CN, —NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ and —SO₃H.

- 10 20. The composition according to claim 18, wherein R, R¹ and R² are independently hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, (C₁-C₄)alkoxy, (C₅-C₆)cycloalkyl, (C₆-C₁₀)cycloalkylalkyl, (C₆)aryl, or (C₇-C₁₀)aralkyl;



- 15 X is O-(C₁-C₇)alkylene, O-(C₂-C₇)alkenylene, (C₁-C₈)alkylene or (C₂-C₈)alkenylene; and
 R⁹ is —NR¹⁰R¹¹.

21. The composition according to claim 19, wherein —Z—X— is



- 20 and R¹ and R² are independently —CH₂CH₃, —CH₂CH=CH₂, —CH₂CH₂CH₃ or cyclohexylmethyl.

22. The composition according to claim 21, wherein wherein aryl is phenyl and aralkyl is benzyl.

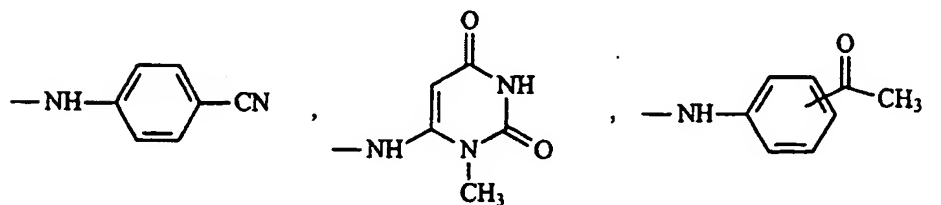
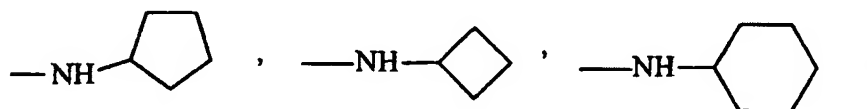
23. The composition according to claim 22, wherein R^9 is phenyl substituted with 1-3 substituents that are independently trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, alkenyl, benzyl, F, Cl, Br, I, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2R^{15}$, $-\text{C(O)}R^{16}$, $-\text{NR}^{13}R^{14}$ or $-\text{C(O)}\text{NR}^{17}R^{18}$, or

5 benzyl, optionally substituted with 1-3 substituents that are independently alkyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, alkenyl, $-\text{OH}$, F, Cl, Br, I, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2R^{15}$, $-\text{C(O)}R^{16}$, $-\text{NR}^{13}R^{14}$ or $-\text{C(O)}\text{NR}^{17}R^{18}$.

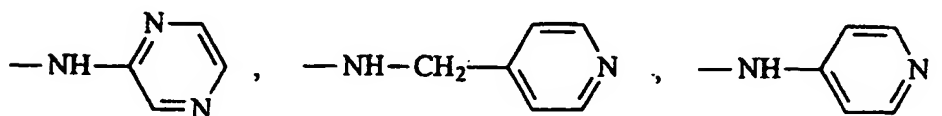
10 24. The composition according to claim 23, wherein R^8 is hydrogen and R^9 is phenyl substituted with 1-3 substituents that are independently F, Cl, Br, I, $-\text{CN}$, $-\text{COOH}$, $-\text{CO}_2\text{CH}_3$, $-\text{C(O)}\text{CH}_2\text{CH}_3$, $-\text{C(O)}\text{CH}_3$, $-\text{C(O)}\text{NH}_2$ or $-\text{C(O)}\text{NHCH}_3$, or

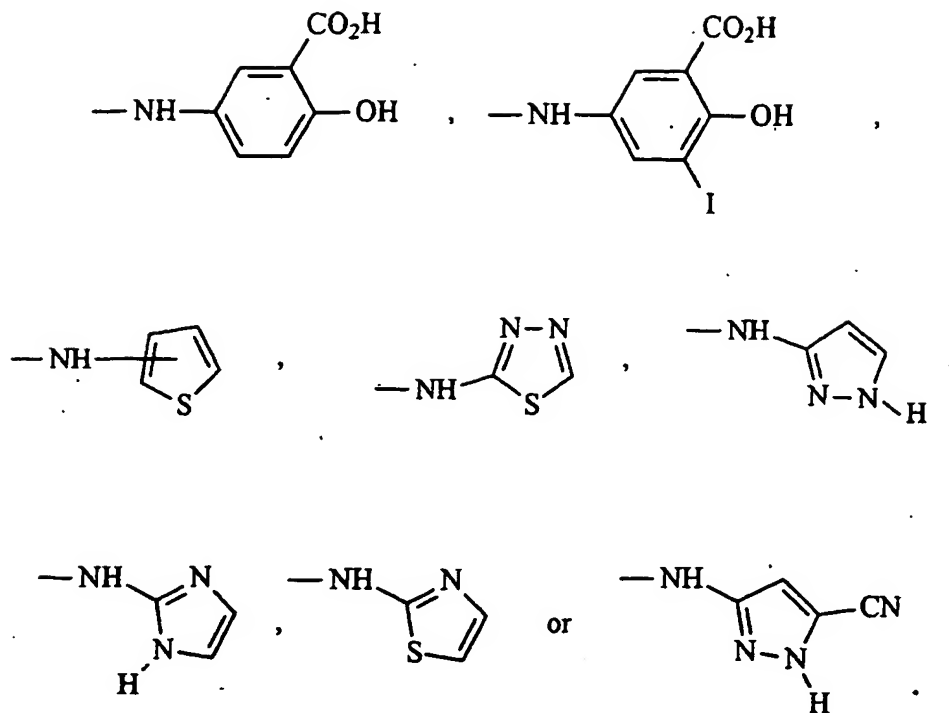
15 benzyl, optionally substituted with 1-3 substituents that are independently $-\text{CH}_2\text{CH}_3$, F, Cl, Br, I, $-\text{CN}$, $-\text{COOH}$, $-\text{CO}_2\text{CH}_3$, $-\text{C(O)}\text{CH}_2\text{CH}_3$, $-\text{C(O)}\text{CH}_3$, $-\text{C(O)}\text{NH}_2$ or $-\text{C(O)}\text{NHCH}_3$.

25. The composition according to claim 21, wherein $-\text{NR}^8R^9$ is:

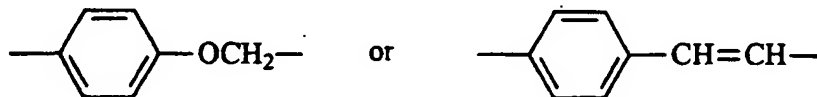


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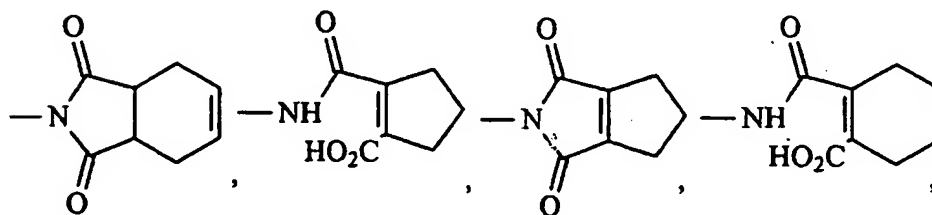
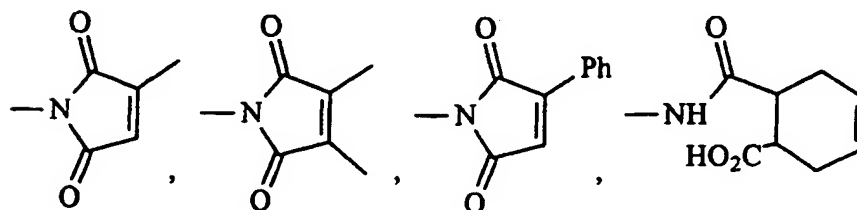
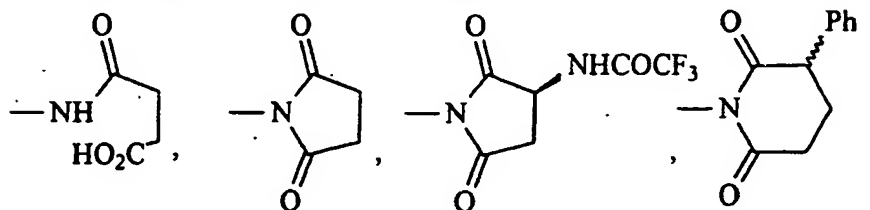
- 5 26. The composition according to claim 25, wherein R and R⁸ are each H, R¹ and R² are each $\text{—CH}_2\text{CH=CH}_2$, and R⁹ is 4-cyanophenyl.
27. The composition according to claim 26, wherein R and R⁸ are each H, R¹ and R² are each $\text{—CH}_2\text{CH}_2\text{CH}_3$, and R⁹ is 3-carboxy-4-hydroxyphenyl or 3-
- 10 acetylphenyl.
28. The composition according to claim 20, wherein —Z—X— is



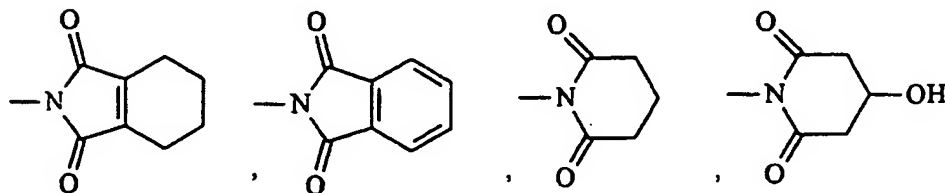
- wherein R¹, and R² are independently $\text{—CH}_2\text{CH}_3$, $\text{—CH}_2\text{CH=CH}_2$,
 15 $\text{—CH}_2\text{CH}_2\text{CH}_3$ or cyclohexylmethyl; and
 R⁸ is hydrogen, aryl or aralkyl.

29. The composition according to claim 28, wherein R^{10} and R^{11} are independently hydrogen, $-C(O)(CH_2)_nCO_2R^{12}$, $-C(O)CR^{21}=CR^{22}CO_2R^{12}$, $-C(O)R^{12}$, $-C(O)(C_3-C_6)cycloalkyl$, $-C(O)(C_3-C_6)cycloalkenyl$ or wherein the R^{10} and R^{11} groups and the nitrogen atom taken together form said
- 5 optionally substituted heterocycle or a heteroaryl ring, and n is 2.

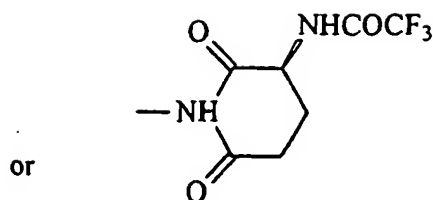
30. The composition of claim 29, wherein R^9 is



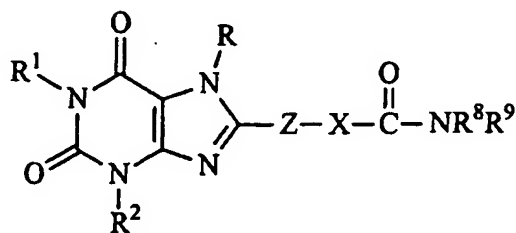
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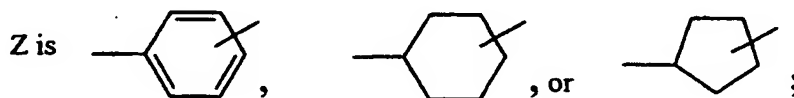


31. A pharmaceutical composition comprising a compound of formula I:



I

wherein R and R¹ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, heterocycle, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or heteroaryl;



X is (C₁-C₈)alkylene, (C₂-C₈)alkenylene, (C₂-C₈)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R⁴)C(O)—, —OC(O)—, —N(R⁵)(R⁶)—, —S—, —S(O)— or —SO₂—,

R² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heterocycle or heteroaryl; wherein R² is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH₂, —NHR⁷, —CN, —COOH and —SO₃H,

wherein R^4 , R^5 , R^6 and R^7 are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl or halo (C_1-C_6) alkyl; and

- wherein R^8 is hydrogen, (C_3-C_8) cycloalkyl, (C_2-C_{16}) cycloalkylalkyl,
 5 (C_7-C_{18}) aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, (C_1-C_8) alkoxy, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, halo, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$
 10 or $-SO_3H$; or

- R^8 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$,
 15 $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

- R^8 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$,
 20 $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; and

- wherein R^9 is (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, (C_7-C_{18}) aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl,
 25 heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ or $-SO_3H$;
 or

- R^9 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl,
 30 (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, halo, $-CN$, $-NO_2$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$, $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$; or

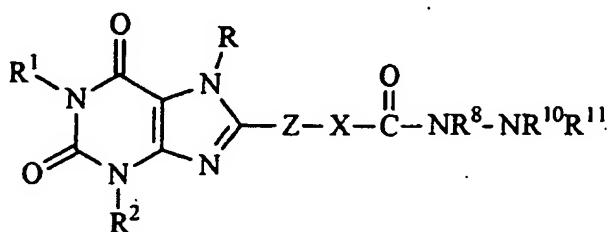
R^9 is (C_6-C_{10}) aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_6) alkyl, (C_2-C_8) alkenyl, (C_7-C_{18}) aralkyl, heteroaryl, $-OR^{15}$, $-CN$, $-NO_2$, $-CO_2R^{15}$, $-OC(O)R^{16}$, $-C(O)R^{16}$, $-NR^{13}R^{14}$, $-N(R^{23})C(O)R^{24}$,
 5 $-C(O)NR^{17}R^{18}$, $-SR^{19}$, $-SO_2R^{20}$ and $-SO_3H$, and

wherein, R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{23} and R^{24} are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl or halo (C_1-C_6) alkyl;

provided that $-NR^8R^9$ is not aminoalkyl or aminodialkyl; and
 10 provided that when R and R^8 are both H, and R^1 and R^2 are both alkyl, R^9 is not 2-hydroxyethyl, 2-thioethyl, 2-haloethyl, 2,2-dimethoxyethyl, 2-acetoxyethyl, 1-methyl-2-phenylethyl, 4-methylphenyl or 4-hydroxyphenyl; or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

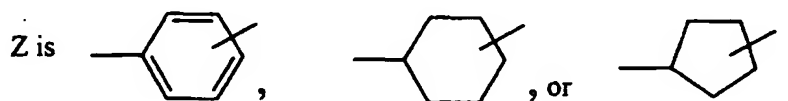
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32. A pharmaceutical composition comprising a compound of formula II:



II

wherein R and R^1 are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_8) alkoxy, (C_3-C_8) cycloalkyl, (C_4-C_{16}) cycloalkylalkyl, heterocycle, (C_6-C_{10}) aryl, (C_7-C_{18}) aralkyl or heteroaryl;
 20



X is (C_1-C_8) alkylene, (C_2-C_8) alkenylene, (C_2-C_8) alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is

optionally replaced with a group having the formula $-\text{O}-$, $-\text{N}(\text{R}^4)\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{N}(\text{R}^5)(\text{R}^6)-$, $-\text{S}-$, $-\text{S}(\text{O})-$ or $-\text{SO}_2-$,

R^2 is hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_8) alkoxy, (C_3-C_8) cycloalkyl, $(\text{C}_4-\text{C}_{16})$ cycloalkylalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heterocycle or heteroaryl; wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NHR}^7$, $-\text{CN}$, $-\text{COOH}$ and $-\text{SO}_3\text{H}$,

wherein R^4 , R^5 , R^6 and R^7 are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl or halo (C_1-C_8) alkyl;

wherein R^8 is hydrogen, (C_3-C_8) cycloalkyl, $(\text{C}_4-\text{C}_{16})$ cycloalkylalkyl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, (C_1-C_8) alkoxy, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, halo, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; or

R^8 is (C_1-C_8) alkyl, substituted with one or more substituents independently selected from the group consisting of oxo, (C_2-C_8) alkenyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; or

R^8 is $(\text{C}_6-\text{C}_{10})$ aryl, substituted with one or more substituents independently selected from the group consisting of (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC}(\text{O})\text{R}^{16}$, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N}(\text{R}^{23})\text{C}(\text{O})\text{R}^{24}$, $-\text{C}(\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; and

wherein R^{10} and R^{11} are independently hydrogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_3-C_8) cycloalkyl, $(\text{C}_6-\text{C}_{10})$ aryl, $(\text{C}_7-\text{C}_{18})$ aralkyl, heteroaryl, $-\text{C}(\text{O})(\text{CH}_2)_n\text{CO}_2\text{R}^{12}$, $-\text{C}(\text{O})\text{CR}^{21}=\text{CR}^{22}(\text{CH}_2)_m\text{CO}_2\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})(\text{C}_3-\text{C}_8)$ cycloalkyl or $-\text{C}(\text{O})(\text{C}_3-\text{C}_8)$ cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C_1-C_8) alkyl, halo (C_1-C_8) alkyl, (C_2-C_8) alkenyl,

- (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H; or the R¹⁰ and R¹¹ groups and the nitrogen atom can be taken together to form a heterocyclic ring or a
- 5 heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C₁-C₈)alkyl, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H; wherein n is 1 to 6, and m is 0
- 10 to 4;

R¹² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heterocycle, or heteroaryl,

- wherein the R¹² group is optionally substituted with one or more
- 15 substituents independently selected from the group consisting of oxo, (C₁-C₈)alkyl, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H;
- wherein R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²³ and R²⁴ are
- 20 independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or halo(C₁-C₆)alkyl;

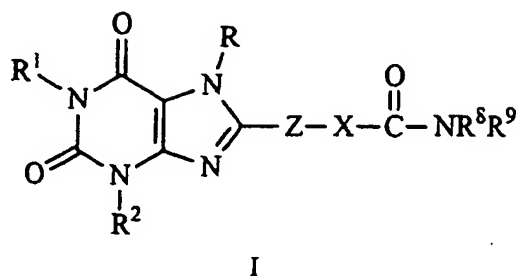
R²¹ and R²² are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl;

- provided that —NR⁸—NR¹⁰R¹¹ is not hydrazino; or
- 25 a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

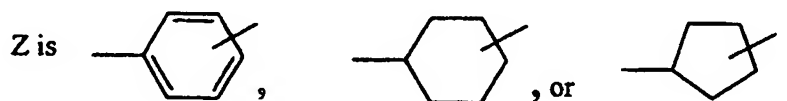
33. A method for treating asthma comprising administering an effective amount of a compound of claim 1, 15 or 16 to a mammal in need of such
- 30 treatment.

34. A method for treating diarrheal diseases, insulin resistance, diabetes, cancer, ischemia/reperfusion injuries, diabetic retinopathy or hyperbaric

oxygen-induced retinopathy, comprising administering an effective amount of a compound of formula I:



wherein R, and R¹ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₀)cycloalkylalkyl, heterocycle, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or heteroaryl;



X is (C₁-C₈)alkylene, (C₂-C₈)alkenylene, (C₂-C₈)alkynylene, wherein one of the carbon atoms in the alkylene, alkenylene or alkynylene groups is optionally replaced with a group having the formula —O—, —N(R⁴)C(O)—, —OC(O)—, —N(R⁵)(R⁶)—, —S—, —S(O)— or —SO₂—,

R² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₁-C₈)alkoxy, (C₃-C₈)cycloalkyl, (C₄-C₁₀)cycloalkylalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heterocycle or heteroaryl; wherein R² is optionally substituted with one or more substituents selected from the group consisting of —OH, —SH, —NH₂, —NHR⁷, —CN, —COOH and —SO₃H,

wherein R⁴, R⁵, R⁶ and R⁷ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or halo(C₁-C₆)alkyl; and

wherein R⁸ is hydrogen, (C₃-C₈)cycloalkyl, (C₄-C₁₀)cycloalkylalkyl, (C₇-C₁₈)aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C₁-C₈)alkyl, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl,

heteroaryl, halo, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC(O)R}^{16}$, $-\text{C(O)R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N(R}^{23})\text{C(O)R}^{24}$, $-\text{C(O)NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$;
or

R^8 is $(\text{C}_1\text{-C}_8)$ alkyl, substituted with one or more substituents

- 5 independently selected from the group consisting of oxo, $(\text{C}_2\text{-C}_8)$ alkenyl, $(\text{C}_6\text{-C}_{10})$ aryl, $(\text{C}_7\text{-C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{OC(O)R}^{16}$, $-\text{C(O)R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N(R}^{23})\text{C(O)R}^{24}$, $-\text{C(O)NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; or

R^8 is $(\text{C}_6\text{-C}_{10})$ aryl, substituted with one or more substituents

- 10 independently selected from the group consisting of $(\text{C}_1\text{-C}_8)$ alkyl, halo $(\text{C}_1\text{-C}_8)$ alkyl, $(\text{C}_2\text{-C}_8)$ alkenyl, $(\text{C}_7\text{-C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC(O)R}^{16}$, $-\text{C(O)R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N(R}^{23})\text{C(O)R}^{24}$, $-\text{C(O)NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; and

wherein R^9 is $-\text{NR}^{10}\text{R}^{11}$, or R^9 is $(\text{C}_3\text{-C}_8)$ cycloalkyl, $(\text{C}_4\text{-C}_{16})$ cyclo-

- 15 alkylalkyl, $(\text{C}_7\text{-C}_{18})$ aralkyl, heterocycle or heteroaryl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, $(\text{C}_1\text{-C}_8)$ alkyl, halo $(\text{C}_1\text{-C}_8)$ alkyl, $(\text{C}_2\text{-C}_8)$ alkenyl, $(\text{C}_6\text{-C}_{10})$ aryl, $(\text{C}_7\text{-C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC(O)R}^{16}$, $-\text{C(O)R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N(R}^{23})\text{C(O)R}^{24}$, $-\text{C(O)NR}^{17}\text{R}^{18}$,
20 $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ or $-\text{SO}_3\text{H}$; or

R^9 is $(\text{C}_1\text{-C}_8)$ alkyl, substituted with one or more substituents

- independently selected from the group consisting of oxo, $(\text{C}_2\text{-C}_8)$ alkenyl, $(\text{C}_6\text{-C}_{10})$ aryl, $(\text{C}_7\text{-C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{OC(O)R}^{16}$, $-\text{C(O)R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N(R}^{23})\text{C(O)R}^{24}$, $-\text{C(O)NR}^{17}\text{R}^{18}$,
25 $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$; or

R^9 is $(\text{C}_6\text{-C}_{10})$ aryl, substituted with one or more substituents

- independently selected from the group consisting of $(\text{C}_1\text{-C}_8)$ alkyl, halo $(\text{C}_1\text{-C}_8)$ alkyl, $(\text{C}_2\text{-C}_8)$ alkenyl, $(\text{C}_7\text{-C}_{18})$ aralkyl, heteroaryl, $-\text{OR}^{15}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^{15}$, $-\text{OC(O)R}^{16}$, $-\text{C(O)R}^{16}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{N(R}^{23})\text{C(O)R}^{24}$,
30 $-\text{C(O)NR}^{17}\text{R}^{18}$, $-\text{SR}^{19}$, $-\text{SO}_2\text{R}^{20}$ and $-\text{SO}_3\text{H}$, and

wherein R^{10} and R^{11} are independently hydrogen, $(\text{C}_1\text{-C}_8)$ alkyl,

$(\text{C}_2\text{-C}_8)$ alkenyl, $(\text{C}_3\text{-C}_8)$ cycloalkyl, $(\text{C}_6\text{-C}_{10})$ aryl, $(\text{C}_7\text{-C}_{18})$ aralkyl, heterocycle, heteroaryl, $-\text{C(O)(CH}_2)_n\text{CO}_2\text{R}^{12}$, $-\text{C(O)CR}^{21}=\text{CR}^{22}(\text{CH}_2)_m\text{CO}_2\text{R}^{12}$,

- C(O)R¹², —C(O)(C₃-C₈)cycloalkyl or —C(O)(C₃-C₈)cycloalkenyl, each optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C₁-C₈)alkyl, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂,
 5 —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H; or the R¹⁰ and R¹¹ groups and the nitrogen atom can be taken together to form a heterocyclic ring or a heteroaryl ring, each ring optionally substituted with one or more substituents, wherein the substituents independently are oxo, (C₁-C₈)alkyl, halo(C₁-C₆)alkyl,
 10 (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heteroaryl, —OR¹⁵, halo, —CN, —NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H; wherein n is 1 to 6, and m is 0 to 4;

- R¹² is hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,
 15 (C₃-C₈)cycloalkyl, (C₄-C₁₆)cycloalkylalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl, heterocycle, or heteroaryl,

- wherein the R¹² group is optionally substituted with one or more substituents independently selected from the group consisting of oxo, (C₁-C₈)alkyl, halo(C₁-C₆)alkyl, (C₂-C₈)alkenyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl,
 20 heteroaryl, —OR¹⁵, halo, —CN, —NO₂, —CO₂R¹⁵, —OC(O)R¹⁶, —C(O)R¹⁶, —NR¹³R¹⁴, —N(R²³)C(O)R²⁴, —C(O)NR¹⁷R¹⁸, —SR¹⁹, —SO₂R²⁰ or —SO₃H;

wherein R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²³ and R²⁴ are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl or halo(C₁-C₆)alkyl;

- 25 wherein R²¹ and R²² are independently hydrogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₇-C₁₈)aralkyl;

or a pharmaceutically acceptable salt thereof to a mammal in need of such treatment.

- 30 35. A therapeutic method for preventing or treating a pathological condition or symptom in a mammal, wherein the activity of adenosine A_{2B} receptors is implicated and antagonism of its action is desired comprising

administering to the mammal an effective amount of a compound of claim 1,
15 or 16.

36. The compound of claim 1, wherein one of the atoms of said compound
5 is replaced by its radionuclide.

37. The compound of claim 36, wherein the radionuclide is tritium, or
radioactive iodine.

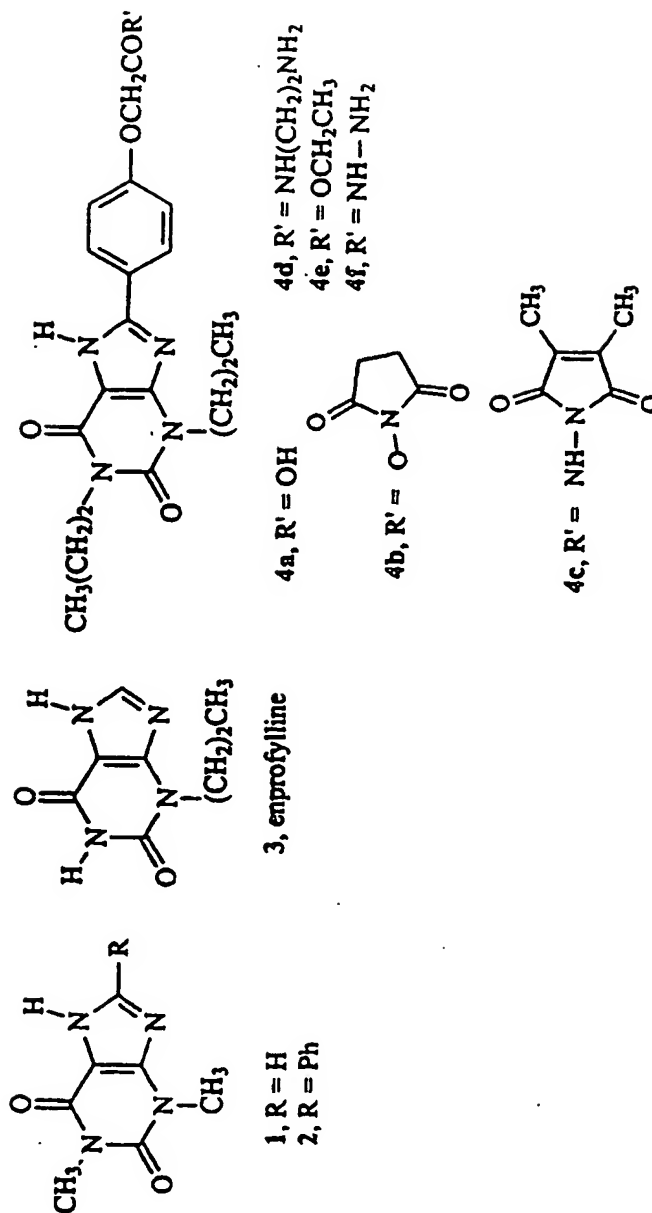


FIG. 1

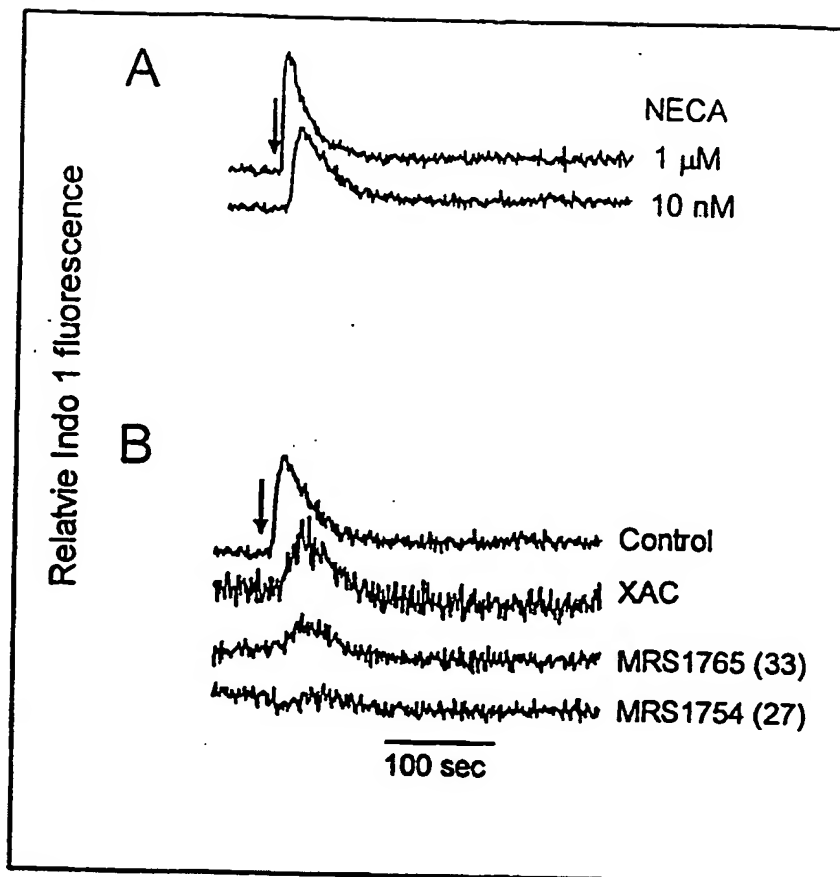
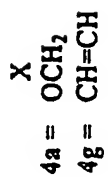
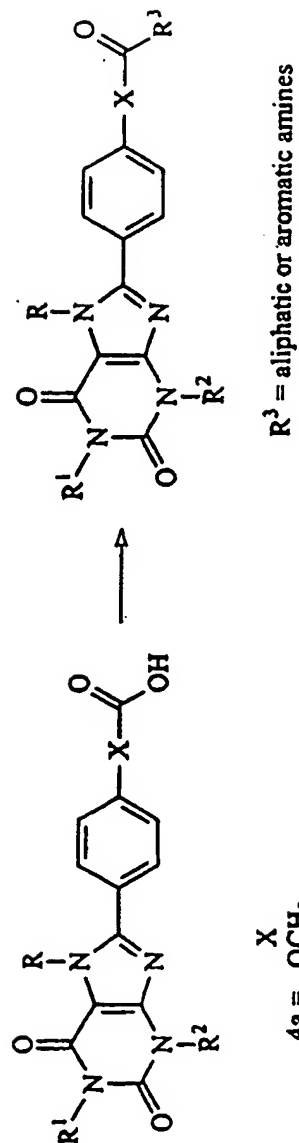


FIG. 2



Reagents: 1) EDAC, DMAP, amines in DMF/CH₂Cl₂; 2) BOP-Cl, triethylamine, amines in CH₂Cl₂; or 3) SOCl₂, amines in pyridine/CH₂Cl₂.

FIG. 3

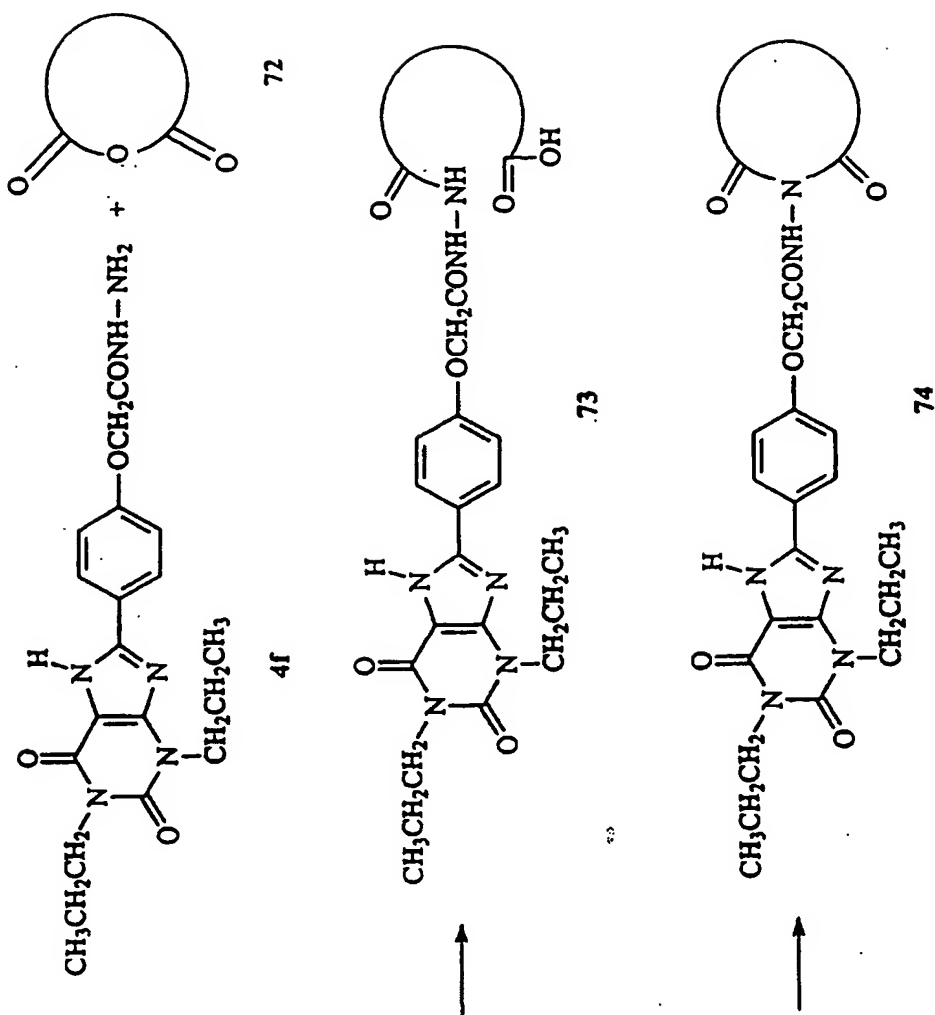


FIG. 4

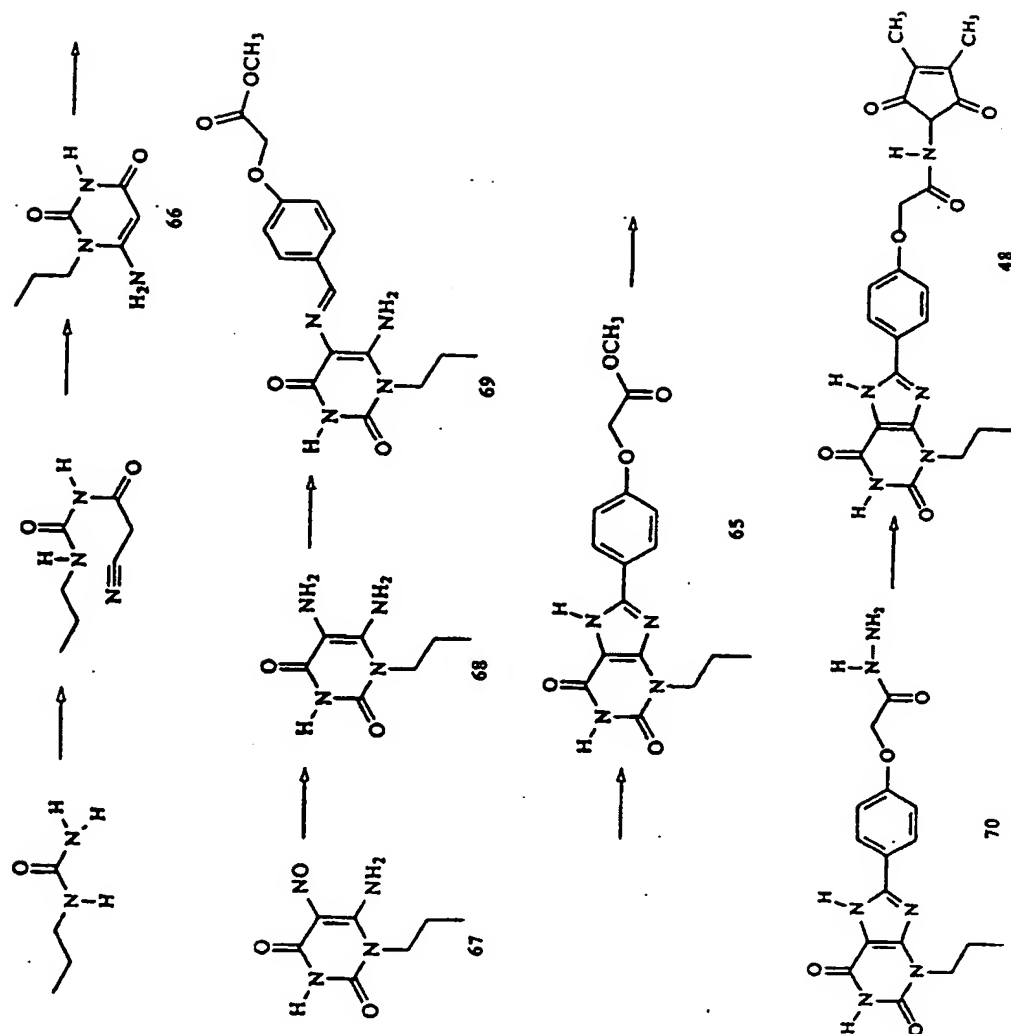
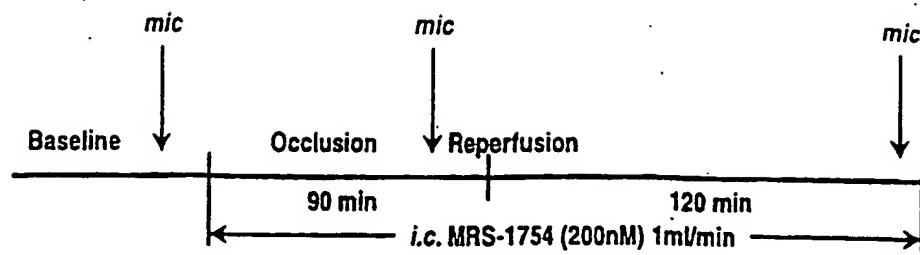


FIG. 5



Blood Sampling from CS

Baseline (x 2), 30 sec, 60 sec, 90 sec, 2 min, 3 min, 5 min, 10 min, 15 min, 30 min

FIG. 6

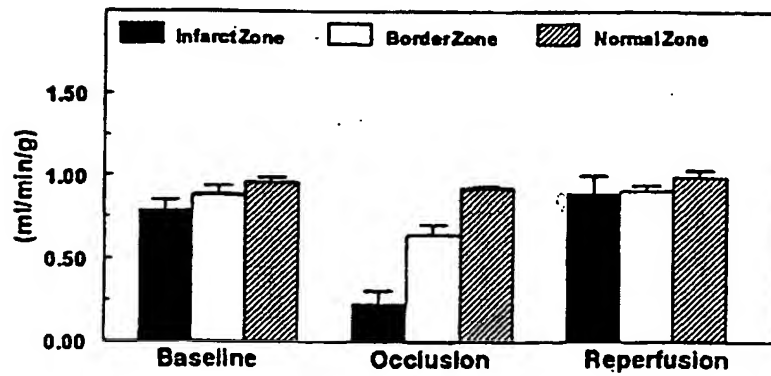


FIG. 7

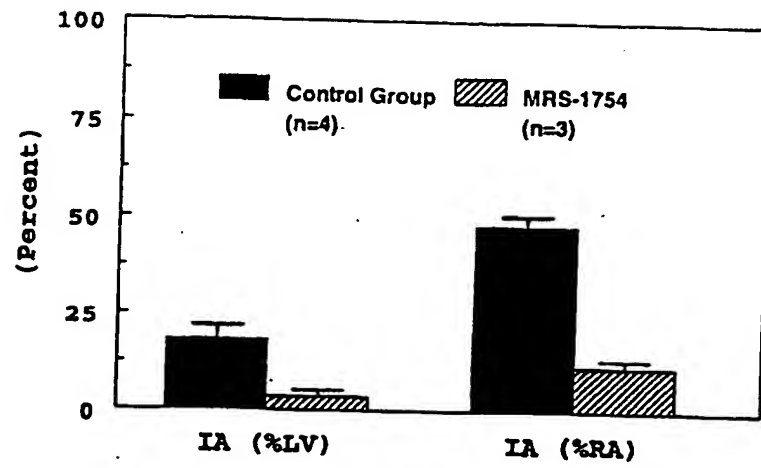
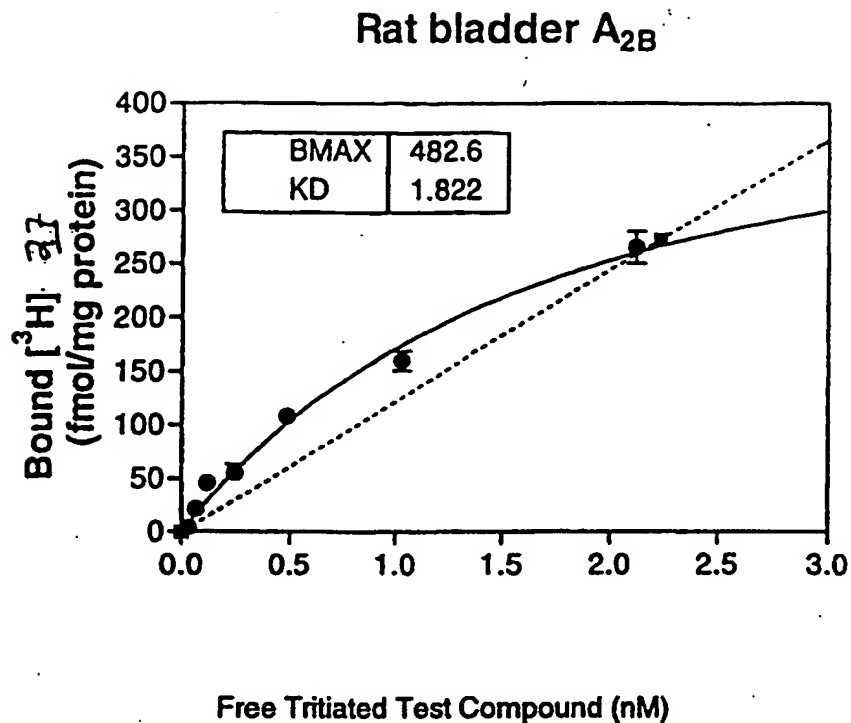


FIG. 8

SUBSTITUTE SHEET (RULE 26)



[³H] 8-[4-(((4-Cyano)phenylcarbamoymethyl)oxy)phenyl]-1,3-di-(n-propyl)xanthine (27).

—— Specific binding (•).
----- Nonspecific binding.

FIG. 9

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A61K 31/505, A61P 11/06

(74) Agent: VIKSNINS, Anna, S.; Schwegman, Lundberg,
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ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ,
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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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ver Spring, MD 20902-3438 (US). KIM, Yong-Chul
[KR/US]; Apartment 202, 12407 Village Square Terrace,
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*For two-letter codes and other abbreviations, refer to the "Guid-
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(54) Title: SUBSTITUTED 8-PHENYLXANTHINES USEFUL AS ANTAGONISTS OF A_{2B} ADENOSINE RECEPTORS

(57) Abstract: The present invention provides compounds and pharmaceutical compositions that are selective antagonists of A_{2B} adenosine receptors (ARs). These compounds and compositions are useful as pharmaceutical agents.

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X,Y	JACOBSON ET AL.: "Functionalized congeners of 1,3-dialkylxanthines..." J.MED.CHEM., vol. 28, no. 9, 1985, pages 1334-1340, XP000942532 table I	1-37

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Z document member of the same patent family

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Authorized officer

Steendijk, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Inter. Nat. Application No.

PCT/US 00/15233

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

Inter. Appl. Application No

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60/151,875 31 August 1999 (31.08.1999) US
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: SUBSTITUTED 8-PHENYLXANTHINES USEFUL AS ANTAGONISTS OF A_{2B} ADENOSINE RECEPTORS

(57) Abstract: The present invention provides compounds and pharmaceutical compositions that are selective antagonists of A_{2B} adenosine receptors (ARs). These compounds and compositions are useful as pharmaceutical agents.